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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-095026- -00000-0000
Fecha: 2010-08-04 14:05:51 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 514

PCT

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. 10-95026

1/2

54. TITULO: **TRIAZOLOPIRIDAZINAS COMO INHIBIDORES DEL PAR1, SU PRODUCCION Y SU USO COMO MEDICAMENTOS**

52. CLASIFICACION INTERNACIONAL: **C07D 487/04, A61K 31/5025, A61P 7/02**

71. SOLICITANTE: **SANOFI-AVENTIS**

DOMICILIO: **174, Avenue de France, 75013 París, FRANCIA**

74. APODERADO: **DR. LUIS PATIÑO LEYVA**

22. BOGOTA, D.C., - 4 AGO. 2010

05-09-2010

26 fls - 31-08-2010

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-095026- -00000-0000

Fecha: 2010-08-04 14:05:51 Dep: 2020 DIR.NUEVASCR
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Act: 411 PRESENTACION Folios: 514

FORMULARIO UNICO DE SOLICITUD DE PATENTES
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

①

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

[X] **Capítulo I** [ ] **Capítulo II**

② **SOLICITANTE (71)**

Nombre: **SANOFI-AVENTIS**

Dirección: **174, avenue de France**
75013 Paris
FRANCIA

Nacionalidad o Domicilio: **París - FRANCIA**

Lugar de Constitución: **FRANCIA**

Teléfono: Fax:
E-mail:

IDENTIFICACIÓN

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual _____

Número _____

③ **REPRESENTANTE O APODERADO**

Nombre: **DR. LUIS PATIÑO LEYVA**

Dirección: **CALLE 94A No. 7A-09**

Teléfono: **7560770** Fax: **7550158**

E-mail: info@castellanosyco.com

IDENTIFICACIÓN

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]
Cual _____

Número **2.930.616** TPA **2.698**

④ **INVENTOR (ES) (72)**

VER ANEXO # 1

⑤ **PCT (86)**

Solicitud Internacional No. **PCT/EP2009/000406** Fecha **23/01/2009**

Publicación Internacional No. **WO 2009/097970 A1** Fecha **13/08/2009**

⑥ **Título (54)** **TRIAZOLOPIRIDAZINAS COMO INHIBIDORES DEL PAR1, SU PRODUCCION Y SU USO COMO MEDICAMENTOS**

⑦ **Clasificación Internacional (51)** **C07D 487/04, A61K 31/5025, A61P 7/02**

⑧ **Prioridad**

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	05/02/2008	08290112,5

⑨ **Comprobantes de pago Nos.** _____ **Fecha** _____

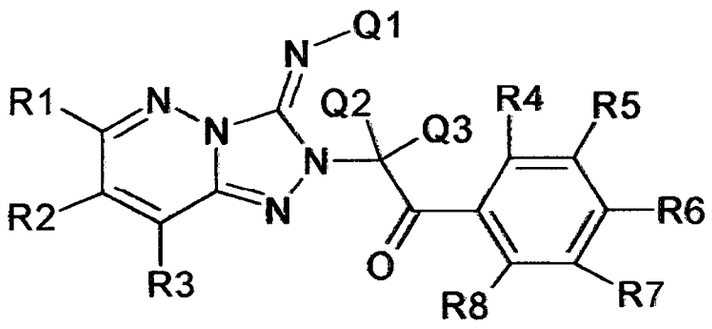
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

00000

(10) Anexos

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [X] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: **Tarjeta Propietario, Extracto para la publicación**

(11) FIGURA CARACTERISTICA:



(I)

(12) Solicito la concesión de la patente,

NOMBRE: **LUIS PATIÑO LEYVA**

FIRMA:

C.C. No. 2.930.616 Bogotá - TPA 2.698 C.S.J.

04 AGO. 2010

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - P20268

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

ANEXO # 1
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   65926 Frankfurt am Main
   ALEMANIA

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 62,283
FECHA : AGOSTO 2 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-095026- -00000-0000

Fecha: 2010-08-04 14:05:51 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 PASENACIONALI
Act: 411 PRESENTACION Folios: 514

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	393932920	02/08/2010	6,593,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

G.HOLLMANN RESTREPO
ABOGADOS LTDA

The undersigned SANOFI AVENTIS...., acting on behalf of and representing of ..... , domiciled in 174 Avenue de France, 75013 PARIS, FRANCE, hereby appoint(s) **LUIS PATIÑO LEYVA** and/or **GUSTAVO HOLLMANN RESTREPO**, domiciled in Bogotá D.C., Republic of Colombia , as our true and legal attorney with the necessary powers:

1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, utility models, industrial designs and models, commercial ensigns and names, trademarks, slogans, health licenses, copyrights and domain names as well as their assignments, extensions, renewals and changes of name; 2) To prepare, apply for, obtain, execute and register contracts, licenses, authorizations and registrations of any kind; 3) To intervene as plaintiff or defendant, in any instance or appeal, before any judge, court, tribunal, corporation, public officer or authority in any judicial, administrative or police action, such as: action dealing with commercial ensigns and names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and working of license agreements; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages, complaints or remarks on all sort of industrial property matters; the performance of precautionary measures, and in any other similar action, measure or appeal related to intellectual property matters.

To this effect, I (we) hereby authorize him to file applications, make descriptions, protests, amendments, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by Law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general, to take, before said authorities, pertinent steps to the above mentioned purposes and take all measures they may deem advisable to protect my (our) interests, with all other necessary legal faculties, and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit.

This power comprises the authority to ratify or confirm on my (our) behalf any action, as well as the faculty of receiving, desisting, transacting, compromising, substituting and revoking substitutions, taking notifications, and appointing judicial or extra-judicial attorneys.

Signed in Paris on this 14day of December of 2006.

MERLIER Josiane, Director Patent Administration

Como Notario Veintiséis del Circulo de Bogotá, hago constar que esta copia coincide con original que se ha presentado Bogotá D.C. - Colombia.

19 JUL 2010

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

G. HOLLMANN RESTREPO
ABOGADOS LTDA

Yo (nosotros) , obrando en nombre propio y representación de, con domicilio en , nombro(amos) a **LUIS PATIÑO LEYVA** y/o **GUSTAVO HOLLMANN RESTREPO** , con domicilio en Bogotá D.C., República de Colombia, apoderado verdadero y legal, con poder especial, amplio y suficiente:

1) Para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, dibujos y modelos industriales, registro de marcas, registro de lemas comerciales, depósito de nombres y enseñas comerciales, registros sanitarios, derechos de autor y nombres de dominio así como sus traspasos, prórrogas, renovaciones y cambios de nombre; 2) Elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clases; 3) Intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas de nombre o enseña comerciales; acciones reivindicatorias; acciones derivadas de la obtención o exploración de licencias; acciones de competencia desleal, demandas penales y civiles; acciones de indemnización de perjuicios, reclamos, u observaciones a cualquier asunto sobre propiedad intelectual; al ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad intelectual.

A este efecto, lo facultamos para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la Ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores dando al descargo respectivo, y en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las facultades necesarias, y por este documento desde ahora declaro(amos) válido y bueno todo cuanto los apoderados hicieren en mi (nuestro) beneficio.

Este poder comprende la facultad de ratificar, o confirmar en mi (nuestro) nombre lo actuado, así como la facultad de recibir, desistir, transigir, comprometer, sustituir y revocar sustituciones, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

Firmado en Paris el de de .

Je soussigné Me Hervé POMMERY
Notaire à Paris, certifie matériellement
la signature de Mme
apposée sur le présent document.
Cette certification ne comporte aucune
vérification de l'exactitude des faits et
actes mentionnés dans le présent document

H. POMMERY, Notaire Associé à PARIS
COUR D'APPEL

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *République française*

Le présent acte public

2. a été signé par Maître POMERY

3. agissant en qualité de Notaire

4. est revêtu du sceau/timbre de son étude

Attesté

5. à PARIS

6. le 20/12/06

7. *par le Procureur général près la Cour d'appel de* PARIS

8. sous n° 174190

9. Sceau : Mme TEPLIER

10. Signature :

L'Apostille confirme seulement l'authenticité de la signature, du sceau o[u] [ins]bre sur le document. Elle ne signifie pas que le contenu du document [lui-]

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19 JUL 2019

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

EN BLANCO
NOTARIA VEINTISEIS

EN BLANCO
NOTARIA VEINTISEIS

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CERTIFICATION

COMPANIES

The undersigned Hervé POMMERY certifies: that the preceding signature(s) reading [illegible] (are) authentic; that the signer(s) at present fill(s) the position of Director of [illegible] that he (they) is (are) empowered to grant this power; and that said company exists, accomplishes its social object and is organized in _____ in accordance with the Laws of France.
All the foregoing facts are known to me, due to my having examined the respective documents to which I attest.

Signed in PARIS on this 14th day of February of 2007.

CERTIFICACIÓN

SOCIEDADES

El(la) infrascrito(a) _____ certifica: que la(s) firma(s) que antecede(n) y dice(n) _____ es (son) auténtica(s); que el (los) signatario(s) desempeña(n) actualmente el cargo(s) de _____ de _____; que tiene(n) facultad para otorgar este poder; y que dicha compañía existe, cumple su objeto social y está organizada en _____ conforme a las Leyes de _____.
Todos los hechos anteriores le constan, por haber examinado los documentos respectivos y de todo ello da fe.

Firmado en _____ el _____ de _____ de _____.

Hervé POMMERY
NOTAIRE

BAILLY POMMERY CAURO
NOTAIRES ASSOCIÉS
D'UNE SCP
30, rue La Boétie - Paris - 8e

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. *République française*
Le présent acte public
2. a été signé par Maître POMMERY
3. agissant en qualité de Notaire
4. est revêtu du sceau/timbre de Ste Etude

Attesté
5. à PARIS
6. le 09/03/2007
7. *par le Procureur général près la Cour d'appel de* PARIS
8. sous n° 17350
9. Sceau :
10. Signature :

L'apostille confirme seulement l'authenticité de la signature, du sceau ou timbre sur le document. Elle ne signifie pas que le contenu du document est [illegible]

APPEL DE PARIS

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EDGAR HERMES PAIXÃO PARDO

Traductor oficial - Traducteur assermenté

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Traducción oficial, parcial, de un documento que me fue presentado en lengua francesa, trabajo realizado en función de mi cargo de traductor oficial de esta ciudad de Santafé de Bogotá.

Contenido del documento:

PODER de SANOFI AVENTIS, 174, Avenue de France, 75013 París, Francia, para Luis Patiño Leyva y/o Gustavo Hollmann Restrepo.

Firma ilegible, Josiane Merlier.

El suscrito, Hervé Pommery, notario en París, autentico la firma de Josiane Merlier. Esta autenticación no implica aceptación del contenido del documento. Firma ilegible y sello de la notaría. París, 19 de febrero de 2007.

Apostillas. (Convención de La Haya del 5 de octubre de 1961).

1. República Francesa. El presente documento público. 2. Fue firmado por el señor Pommery. 3. Actuando en calidad de notario. 4. Lleva el sello de la notaría.

CERTIFICADO:

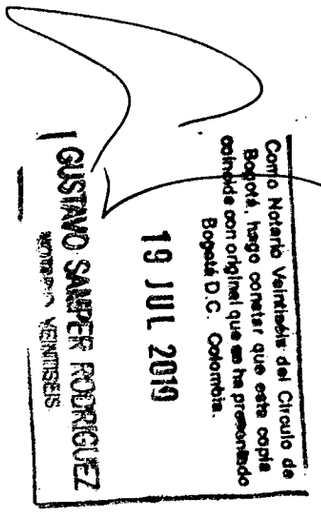
5. En París, 6. El 20 de diciembre de 2006 y el 22 de febrero de 2007. 7. Por el Procurador General de la Corte de Apelaciones de París, 8. bajo los números **174190** y **173350**. 9. Sello de la Corte. 10. Firma ilegible.

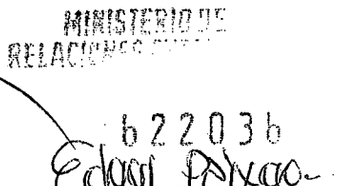
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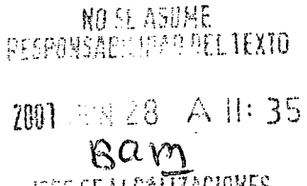
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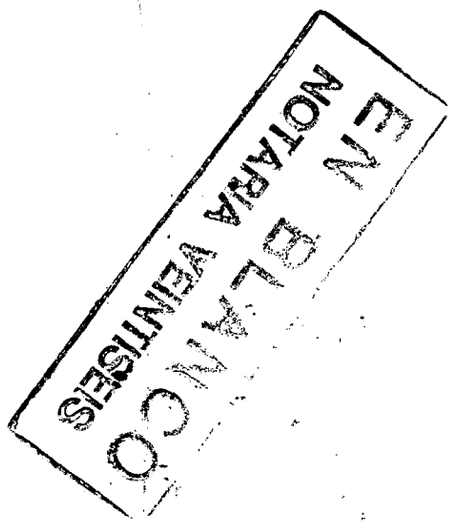
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19 JUL 2010
GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

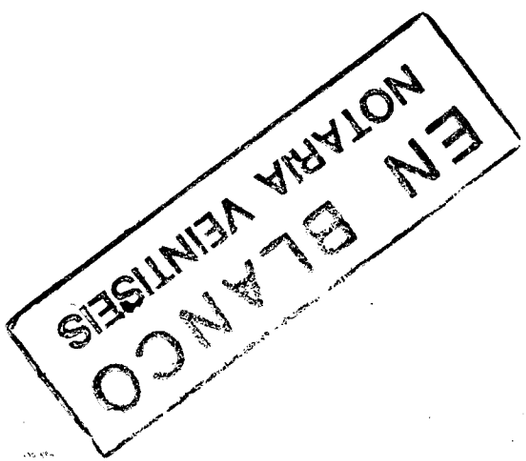
Edgar Hermes Paixão Pardo
Traductor Español
Ley 1306 Minjusticia

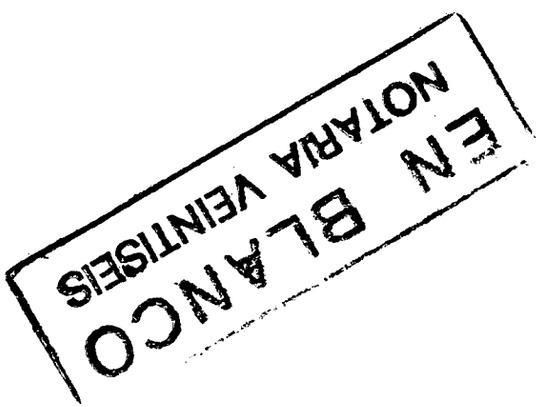

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS
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Bogotá D.C. Colombia.
19 JUL 2019


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RELACIONES
622036
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS


NO SE ASUME
RESPONSABILIDAD DEL TEXTO
2001
28 A 11:35
JEFE DE LEGALIZACIONES
BOGOTA D.C.


EN BLANCO
NOTARIA VEINTISEIS


EN BLANCO
NOTARIA VEINTISEIS


EN BLANCO
NOTARIA VEINTISEIS

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 August 2009 (13.08.2009)

PCT

(10) International Publication Number
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C07D 487/04 (2006.01) *A61P 7/02* (2006.01)
A61K 31/5025 (2006.01)

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(25) Filing Language: German

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(30) Priority Data:
08290112.5 5 February 2008 (05.02.2008) EP

(71) Applicant *(for all designated States except US)*: SANOFI-AVENTIS [FR/FR]; 174, avenue de France, F-75013 Paris (FR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HEINELT, Uwe [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). WEHNER, Volkmar [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). HERRMANN, Matthias [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). SCHOENAFINGER, Karl [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). STEINHAGEN, Henning [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). SCHEIPER, Bodo [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE).

(74) Agent: THEN, Johann; c/o Sanofi-Aventis Deutschland GmbH, Patents Germany, Industriepark Höchst, Geb. K 801, 65926 Frankfurt am Main (DE).

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

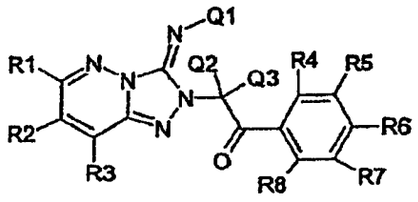
(84) Designated states *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS,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

Published:
- *with international search report (Article 21 (3))*

As printed

(54) Title: TRIAZOLOPYRIDAZINES AS PAR1 INHIBITORS, PRODUCTION THEREOF, AND USE AS MEDICAMENTS

(54) Bezeichnung: TRIAZOLOPYRIDAZINE ALS PAR1-INHIBITOREN, IHRE HERSTELLUNG UND VERWENDUNG ALS ARZNEIMITTEL



(I)

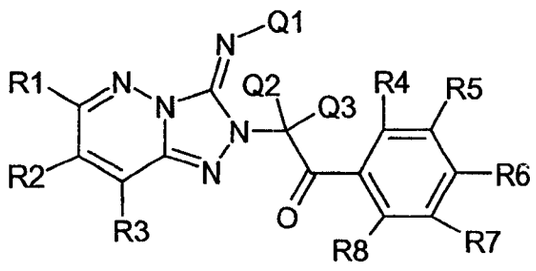
(57) Abstract: The invention relates to compounds of formula (I) that have an antithrombotic activity and particularly inhibit protease-activated receptor 1, methods for the production thereof, and the use thereof as medicaments.

(57) Zusammenfassung: Die Erfindung betrifft Verbindungen der Formel (I) mit antithrombotischer Aktivität, die insbesondere den Protease-aktivierten Rezeptor 1 inhibieren, Verfahren zu ihrer Herstellung und Verwendung derselben als Arzneimittel.

WO 2009/097970 A1

Triazolopyridazines as PAR1 inhibitors, production thereof, and use as medicaments

The invention relates to novel compounds of the formula I



(I)

where R1, R2, R3, R4, R5, R6, R7, R8, Q1, Q2 and Q3 are each as defined below. The compounds of the formula I have antithrombotic activity and inhibit especially protease-activated receptor 1 (PAR1). The invention further relates to a process for preparing the compound of the formula I and to the use thereof as a medicament.

Protease-activated receptor 1 (PAR1) is a thrombin receptor which belongs to the class of G protein-coupled receptors (GPCR). The gene for PAR1 is located on chromosome 5q13, consists of two exons and covers a region of about 27 kb.

PAR1 is expressed inter alia in endothelial cells, smooth muscle cells, fibroblasts, neurons and human blood platelets. On blood platelets, PAR1 is an important receptor of signal transmission and is involved in initiating the aggregation of blood platelets.

Activation of the PARs takes place by proteolytic elimination of part of the N terminus of the PARs, thus exposing a new N-terminal sequence which then activates the receptor (Pharmacol Rev 54:203-217, 2002).

The coagulation of blood is a process for controlling blood flow which is essential for the survival of mammals. The process of coagulation and the subsequent breakup of the clot after wound healing has taken place starts after damage to a vessel and can be divided into four phases:

1. The phase of vascular constriction: the blood loss into the damaged area is reduced thereby.

2. The next phase is that of platelet adhesion to the exposed collagen in the subendothelium. This primary adhesion to the matrix activates the platelets, which then secrete various activators which lead to enhancement of the activation. These activators additionally stimulate further recruitment of new platelets to the site of vessel damage and promote platelet aggregation. The platelets aggregate at the site of vessel wall damage and form a still loose platelet plug. Activation of platelets further leads to presentation of phosphatidylserine and phosphatidylinositol along the cell membrane surfaces. Exposure of these phospholipids is essential for binding and activating the multienzyme complexes of the coagulation cascade.

3. The initially still loose platelet aggregate is crosslinked by fibrin. If the thrombus comprises only platelets and fibrin, it is a white thrombus. If red blood corpuscles are additionally present, it is a red thrombus.

4. After wound healing, the thrombus is broken up by the action of the protein plasmin.

Two alternative pathways lead to the formation of a fibrin clot, the intrinsic and the extrinsic pathway. These pathways are initiated by different mechanisms, but in a later phase they converge to a common pathway of the coagulation cascade. Formation of a red thrombus or a clot on the basis of a vessel wall abnormality without wound is the result of the intrinsic pathway. Fibrin clot formation as response to tissue damage or injury is the result of the extrinsic pathway. Both pathways include a relatively large number of proteins which are known as coagulation factors.

The intrinsic pathway requires coagulation factors VIII, IX, X, XI and XII and prekallikrein, high molecular weight kininogen, calcium ions and phospholipids from platelets. Each of these proteins leads to activation of factor X.

The intrinsic pathway is initiated when prekallikrein, high molecular weight kininogen, factor XI and XII bind to a negatively charged surface. This moment is referred to as the contact phase. Exposure to a vessel wall collagen is the primary stimulus of the contact phase. The result of the contact phase processes is conversion of prekallekrein into kallekrein, which in

turn activates factor XII. Factor XIIa hydrolyzes further prekallekrein to kallekrein, so that the result is activation. As the activation of factor XII increases there is activation of factor XI which leads to release of bradykinin, a vasodilator. The initial phase of vasoconstriction is terminated thereby. Bradykinin is produced from the high molecular weight kininogen. In the presence of Ca^{2+} ions, factor XIa activates factor IX. Factor IX is a proenzyme which contains vitamin K-dependent, c-carboxyglutamate (GLA) residues. The serine protease activity becomes evident after Ca^{2+} ions have bound to these GLA residues. Several of the serine proteases in the blood coagulation cascade (factors II, VII, IX and X) contain such vitamin K-dependent GLA residues. Factor IXa cleaves factor X and leads to activation to factor Xa. The precondition for the formation of factor IXa is the formation of a protease complex of Ca^{2+} ions and factors VIIIa, IXa and X on the surface of activated platelets. One of the reactions of activated platelets is the presentation of phosphatidylserine and phosphatidylinositol along the surfaces. Formation of the protease complex is made possible by exposure of these phospholipids. In this process, factor VIII acts as a receptor for factors IXa and X. Factor VIII therefore represents a cofactor in the coagulation cascade. Activation of factor VIII with formation of factor VIIIa, the actual receptor, requires only a minimal amount of thrombin. As the concentration of thrombin increases, factor VIIIa is finally cleaved further, and inactivated, by thrombin. This dual activity of thrombin in relation to factor VIII leads to the protease complex formation being self-limiting and thus the blood coagulation being localized.

PAR1 and PAR4 play a central role in the activation of human blood platelets by thrombin; activation of these receptors leads to morphological changes in blood platelets, release of ADP and aggregation of the blood platelets (Nature 413:26-27, 2001).

PAR1 inhibitors are described for example in the European patent applications EP1391451 or EP1391452, the US patent applications US 6,063,847 and US 2004/152736, and the international application WO 03/089428.

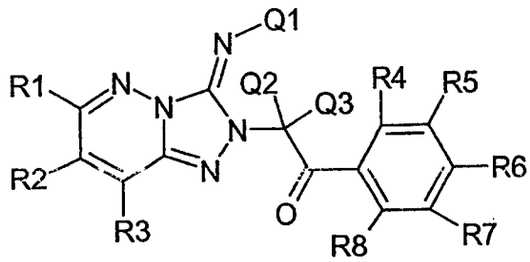
The compounds of the formula I show a high specific inhibition of protease-activated receptor 1 and are notable, compared to compounds from EP1391451, for better membrane permeability, for example through cells of the intestine wall, which can contribute to better

bioavailability.

The compounds of the formula I are therefore suitable for prophylactic and therapeutic use in humans suffering from disorders associated with thromboses, embolisms, hypercoagulability or fibrotic alterations. Examples of such disorders are thrombosis, deep vein thrombosis, pulmonary embolisms, cerebral infarction, myocardial infarction, high blood pressure, inflammatory disorders, rheumatism, asthma, glomerulonephritis or osteoporosis. The compounds of the formula I can be employed for secondary prevention and are suitable both for acute and for long-term therapy.

The compounds of the formula I can also be employed in combination with active ingredients which act by antithrombotic principles different from PAR1.

1) The invention therefore relates to a compound of the formula I



(I)

and/or any stereoisomeric or tautomeric forms of the compound of the formula I and/or mixtures of these forms in any ratio, and/or a physiologically compatible salt of the compound of the formula I, where

Q1 is a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where alkyl and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

Q2 and Q3 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl or -(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R1, R2 and R3 are the same or different and are each independently

a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-C(O)-N(R11)-R12, -(C_0-C_4)-alkylene-C(O)-O-R11, -(C_0-C_4)-alkylene-C(O)-R11, -(C_0-C_4)-alkylene-N(R11)-R12, -(C_0-C_4)-alkylene-N(R11)-C(O)-R12, halogen, OH, -CN, $-NO_2$, $-SO_2CH_3$, $-SO_2CF_3$, $-SF_5$, -Si[-(C_1-C_4)-alkyl]$_3$, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl, -O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, -(C_4-C_{15})-Het,

where Het is unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl,

where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, -(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl,

-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_3-C_6)-cycloalkyl, or

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R1 and R2 or R2 and R3, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of

these atoms are replaced by nitrogen, oxygen or sulfur atoms, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine,

R11 and R12 are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, -SO_2CH_3 or -SO_2CF_3, where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R11 and R12 in the "N(R11)-R12" and "N(R11)-C(O)-R12" fragments represent a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-C(O)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine,

R4, R5, R6, R7 and R8 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -CN, -NO_2, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(CO)-N(R21)-R22,

$-SO_2CH_3$, $-SO_2CF_3$, $-(C_0-C_4)$-alkylene-C(O)-O-R21, halogen, $-SF_5$, $-(C_0-C_4)$-alkylene-C(O)-R21, $-(C_0-C_4)$-alkylene-N(R21)-R22, $-(C_0-C_4)$-alkylene-N(R21)-C(O)-R22, $-(C_1-C_6)$-alkylene-O-(C_1-C_6)-alkyl, $-(C_0-C_6)$-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, $-Si[-(C_1-C_4)\text{-alkyl}]_3$, $-(C_0-C_6)$-alkylene-O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, $-(C_0-C_6)$-alkylene-O-(C_0-C_6)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, $-(C_1-C_4)$-alkyl, OH, $-(C_3-C_6)$-cycloalkyl or -O-(C_3-C_6)-cycloalkyl, or $-(C_4-C_{15})$-Het where Het is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, $-(C_1-C_4)$-alkyl, OH, $-(C_3-C_6)$-cycloalkyl or -O-(C_3-C_6)-cycloalkyl,

where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by $-(C_1-C_4)$-alkyl, $-(C_3-C_6)$-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, $-(C_6-C_{14})$-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, $-(C_1-C_4)$-alkyl, $-(C_3-C_6)$-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl,

$-(C_4-C_{15})$-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, $-(C_1-C_4)$-alkyl, $-(C_3-C_6)$-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_3-C_6)-cycloalkyl,

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R4 and R5, R5 and R6, R6 and R7 or R7 and R8, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of these atoms are replaced by nitrogen, oxygen or sulfur atoms, where the ring is unsubstituted or mono- or disubstituted independently by $-(C_1-C_4)$-alkyl, $-(C_3-C_6)$-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine,

R21 and R22 are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl,

-(C_0-C_4)-alkylene-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl,

$-SO_2CH_3$ or $-SO_2CF_3$,

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R21 and R22 in the "N(R21)-R22" and "N(R21)-C(O)-R22" fragments represent a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-C(O)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine.

2) Preference is given to a compound of the formula I wherein

Q1, Q2 and Q3 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl or -(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R1, R2 and R3 are the same or different and are each independently

hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-C(O)-N(R11)-R12, -(C_0-C_4)-alkylene-C(O)-O-R11, -(C_0-C_4)-alkylene-C(O)-R11,

-(C_0-C_4)-alkylene-N(R11)-R12, -(C_0-C_4)-alkylene-N(R11)-C(O)-R12, halogen, OH, -CN, $-NO_2$, $-SO_2CH_3$, $-SO_2CF_3$, $-SF_5$, -Si[-(C_1-C_4)-alkyl]$_3$, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl, -O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, -(C_4-C_{15})-Het, where Het is unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl,

where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, -(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl,

-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_3-C_6)-cycloalkyl, or

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine,

with the proviso that at least one R1, R2 or R3 is not a hydrogen atom or

R1 and R2 or R2 and R3, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of these atoms are replaced by nitrogen, oxygen or sulfur atoms, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring, in alkyl or cycloalkyl may be replaced

by fluorine,

R11 and R12 are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl,

-(C_0-C_4)-alkylene-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl,

-SO_2CH_3 or -SO_2CF_3,

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R11 and R12 in the "N(R11)-R12" and "N(R11)-C(O)-R12" fragments represent a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-(CO)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R4, R5, R6, R7 and R8 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -CN, -NO_2, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(CO)-N(R21)-R22, -SO_2CH_3, -SO_2CF_3, -(C_0-C_4)-alkylene-C(O)-O-R21, halogen, -SF_5, -(C_0-C_4)-alkylene-C(O)-R21, -(C_0-C_4)-alkylene-N(R21)-R22, -(C_0-C_4)-alkylene-N(R21)-C(O)-R22, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -(C_0-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -Si[-(C_1-C_4)-alkyl]$_3$, -(C_0-C_6)-alkylene-O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, -(C_0-C_6)-alkylene-O-(C_0-C_6)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or

mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl, or -(C_4-C_{15})-Het where Het is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl,

where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, -(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl,

-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_3-C_6)-cycloalkyl, or

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine,

with the proviso that at least one R4, R5, R6, R7 or R8 is not a hydrogen atom, or

R4 and R5, R5 and R6, R6 and R7 or R7 and R8, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of these atoms are replaced by nitrogen, oxygen or sulfur atoms, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine,

R21 and R22 are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl,

-(C_0-C_4)-alkylene-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, $-SO_2CH_3$ or $-SO_2CF_3$, where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R21 and R22 in the "N(R21)-R22" and "N(R21)-C(O)-R22" fragments represent a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-C(O)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine.

3) Particular preference is given to a compound of the formula I, wherein

Q1, Q2 and Q3 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl or -(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R1, R2 and R3 are the same or different and are each independently

a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-C(O)-N(R11)-R12, -(C_0-C_4)-alkylene-C(O)-O-R11, -(C_0-C_4)-alkylene-C(O)-R11, -(C_0-C_4)-alkylene-N(R11)-R12, -(C_0-C_4)-alkylene-N(R11)-C(O)-R12, halogen, OH, -CN, $-NO_2$, $-SO_2CH_3$, -Si[-(C_1-C_4)-alkyl]$_3$, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, -O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, -(C_4-C_{15})-Het or -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl,

where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine,

with the proviso that at least one R1, R2 or R3 is not a hydrogen atom or

R1 and R2 or R2 and R3, together with the ring atoms to which they are each bonded, form a ring selected from the group of 2,3,5,6,7,8-hexahydro-1,2,3a,4,5,8-hexaaza-cyclopenta[b]naphthalene; 2,6,7,8-tetrahydro-3H-5-oxa-1,2,3a,4,8-pentaaza-cyclopenta[b]naphthalene; 2,3,6,7-tetrahydro-5,8-dioxa-1,2,3a,4-tetraaza-cyclopenta[b]naphthalene; 2,3,6,7-tetrahydro-5H-8-oxa-1,2,3a,4,5-pentaaza-cyclopenta[b]naphthalene; 2,6,7,8-tetrahydro-3H-5-thia-1,2,3a,4,8-pentaaza-cyclopenta[b]naphthalene; 2,3,6,7,8,9-hexahydro-1,2,3a,4,6,9-hexaaza-cyclopenta[a]-naphthalene; 2,3-dihydro-5,7-dioxa-1,2,3a,4-tetraaza-s-indacene; 2,6,7,8-tetrahydro-3H-cyclopenta[e][1,2,4]triazolo[4,3-b]pyridazine; 2,7,8,9-tetrahydro-3H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazine and 2,3,6a,9a-tetrahydro-[1,3]dioxolo[4,5-d][1,2,4]triazolo[4,3-b]pyridazine, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R11 and R12 are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, -(C_0-C_4)-alkylene-(C_4-C_{15})-Het, -SO_2CH_3 or -SO_2CF_3,

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R11 and R12 in the "N(R11)-R12" and "N(R11)-C(O)-R12" fragments represent a 5- to 8-membered ring selected from the group of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, morpholinyl, thiomorpholinyl, pyrrolidine-2.5-dionyl, piperidine-2,6-dionyl, piperazine-2,6-dionyl, morpholine-3,5-dionyl, pyrrolidin-2-onyl, piperidin-2-onyl, piperazin-2-onyl and morpholin-3-onyl, where the ring is

unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R4, R5, R6, R7 and R8 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -CN, -NO_2, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(CO)-N(R21)-R22, -SO_2CH_3, -SO_2CF_3, -(C_0-C_4)-alkylene-C(O)-O-R21, halogen, -SF_5, -(C_0-C_4)-alkylene-C(O)-R21, -(C_0-C_4)-alkylene-N(R21)-R22, -(C_0-C_4)-alkylene-N(R21)-C(O)-R22, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -(C_0-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -Si[-(C_1-C_4)-alkyl]$_3$, -(C_0-C_6)-alkylene-O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, -(C_0-C_6)-alkylene-O-(C_0-C_6)-alkylene-(C_6-C_{14})-aryl or -(C_4-C_{15})-Het,

where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, -(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl,

-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_3-C_6)-cycloalkyl, or

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine,

with the proviso that at least one R4, R5, R6, R7 or R8 is not a hydrogen atom, or

R4 and R5, R5 and R6, R6 and R7 or R7 and R8, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring selected from the group of 2,3-dihydrobenzo[1,4]dioxin; 3,4-dihydro-2H-benzo[1,4]oxazine; 1,2,3,4-tetrahydro-

quinoxaline; benzo[1,3]dioxole; 3,4-dihydro-2H-benzo[1,4]thiazine and 2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine,

where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R21 and R22 are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, -(C_0-C_4)-alkylene-(C_4-C_{15})-Het, $-SO_2CH_3$ or $-SO_2CF_3$, where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R21 and R22 in the "N(R21)-R22" and "N(R21)-C(O)-R22" fragments represent a 5- to 8-membered ring selected from the group of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, morpholinyl, thiomorpholinyl, pyrrolidine-2,5-dionyl, piperidine-2,6-dionyl, piperazine-2,6-dionyl, morpholine-3,5-dionyl, pyrrolidin-2-onyl, piperidin-2-onyl, piperazin-2-onyl and morpholin-3-onyl, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine.

4) The invention further relates to a compound of the formula I, wherein

Q1, Q2 and Q3 are the same and are each a hydrogen atom,

R1, R2 and R3 are the same or different and are each independently

hydrogen atom, -(C_1-C_6)-alkyl, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-C(O)-N(R11)-R12, -(C_0-C_4)-alkylene-N(R11)-R12, halogen, -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_0-C_4)-alkylenephenyl or -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl,

where alkyl or alkylene is in each case unsubstituted or mono- or disubstituted by -O-(C_1-C_6)-alkyl,

where some or all of the hydrogen atoms in alkyl or alkylene may be replaced by

fluorine,

with the proviso that at least one R1, R2 or R3 is not a hydrogen atom,

R11 and R12 are each independently a hydrogen atom or -(C_1-C_6)-alkyl, or

R11 and R12 in the "N(R11)-R12" fragment is a 5- to 8-membered ring selected from the group of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, imidazolyl, morpholinyl, thiomorpholinyl, pyrrolidine-2.5-dionyl, piperidine-2,6-dionyl, piperazine-2,6-dionyl, morpholine-3,5-dionyl, pyrrolidin-2-onyl, piperidin-2-onyl, piperazin-2-onyl and morpholin-3-onyl,

R4, R5, R6, R7 and R8 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl, OH, -O-(C_1-C_8)-alkyl, halogen, -SF_5, -(C_0-C_4)-alkylene-N(R21)-R22, -(C_0-C_4)-alkylene-N(R21)-C(O)-R22, -CF_3, -(C_0-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -(C_0-C_6)-alkylene-O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, or -(C_0-C_6)-alkylene-O-(C_0-C_6)-alkylenephenyl,

where alkyl or alkylene is in each case unsubstituted or mono- or disubstituted by -O-(C_1-C_6)-alkyl,

with the proviso that at least one R4, R5, R6, R7 or R8 is not a hydrogen atom, or

R4 and R5, R5 and R6, R6 or R7 and R7 and R8, together with the ring atoms to which they are each bonded, form a five- to eight-membered ring selected from the group of 2,3-dihydrobenzo[1,4]dioxin; 3,4-dihydro-2H-benzo[1,4]oxazine; 1,2,3,4-tetrahydro-quinoxaline; benzo[1,3]dioxole; 3,4-dihydro-2H-benzo[1,4]thiazine and 2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine,

where the ring is unsubstituted or mono- or disubstituted by -(C_1-C_4)-alkyl,

R21 and R22 are each independently a hydrogen atom or -(C_1-C_6)-alkyl, or

R21 and R22 in the "N(R21)-R22" fragment represent a 5- to 8-membered ring selected from the group of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, imidazolyl, morpholinyl, thiomorpholinyl, pyrrolidine-2.5-dionyl, piperidine-2,6-dionyl, piperazine-2,6-dionyl, morpholine-3,5-dionyl, pyrrolidin-2-onyl, piperidin-2-onyl, piperazin-2-onyl and morpholin-3-onyl.

5) Exceptionally preferred are compounds of the formula I including the following compounds:

2-(6-chloro-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(3,5-di-tert-butyl-4-hydroxyphenyl)ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-isopropoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-methoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(4-methoxy-3-morpholin-4-yl-5-trifluoromethylphenyl)ethanone, N-[3-[2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-acetyl]-5-(pentafluorosulfanyl)phenyl]-N-methylacetamide,

N-[3-[2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-acetyl]-5-(pentafluorosulfanyl)phenyl]acetamide as the trifluoroacetic acid salt,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone as the trifluoroacetic acid salt, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclopentyloxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclobutoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-phenoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

2-(6-benzyloxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclohexyloxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[3-imino-6-(2,2,2-trifluoroethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone as the trifluoroacetic acid salt,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclopropylmethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methylamino-5-(pentafluorosulfanyl)phenyl]ethanone,

2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone,

1-(3-tert-butyl-5-ethoxymethylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-cyclopropylmethoxymethylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-4,5-diethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-ethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-propoxymethylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-4,5-bis(cyclopropylmethoxy)phenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-(3-methoxy-5-trifluoromethylphenyl)ethanone,

1-(3-tert-butyl-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-cyclopropylmethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-cyclobutylmethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-benzyloxymethyl-5-tert-butylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-cyclohexylmethoxy-4,5-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

2-(6-butoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(3-tert-butyl-5-methoxymethylphenyl)ethanone,

1-(3-chloro-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(8-tert-butyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone as the trifluoroacetic acid salt,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-piperidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-diethylamino-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-(3-isopropyl-5-methoxyphenyl)ethanone,

1-(3-cyclohexylmethoxy-5-ethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-bromo-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-[3-(3,3-dimethylbutoxy)-5-methoxyphenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-[3-(3,3-dimethylbutoxy)-5-ethoxyphenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-cyclohexylmethoxy-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-bromo-4,5-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

2-(6-diethylamino-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-morpholin-4-yl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-imidazol-1-yl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

1-(5-bromo-2,3-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-methoxyphenyl)-2-{3-imino-6-[2-(2-methoxyethoxy)ethoxy]-[1,2,4]triazolo[4,3-b]pyridazin-2-yl}ethanone,

1-(3-chloro-4,5-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-diethylamino-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone as the trifluoroacetic acid salt,

1-[3-tert-butyl-5-(2-methoxyethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-methoxyphenyl)-2-[3-imino-6-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-methoxymethylphenyl)-2-[3-imino-6-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-morpholin-4-yl-5-(pentafluorosulfanyl)phenyl]ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-(5-methoxy-3-pentafluorosulfanylphenyl)ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

1-[3-tert-butyl-5-(2-methoxyethoxymethyl)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-(2-methoxyethoxy)-5-(pentafluorosulfanyl)phenyl]ethanone,

2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone,

2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-(3-methoxypropoxy)-5-(pentafluorosulfanyl)phenyl]ethanone,

N,N-diethyl-2-[2-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-oxoethyl]-6-chloro-3-imino-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxamide,

N,N-diethyl-6-chloro-3-imino-2-{2-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-2-oxoethyl}-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxamide,

2-(6-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

1-[3-tert-butyl-5-(3-methoxypropoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-[3-tert-butyl-5-(2-methoxyethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-cyclopropylmethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-(3-tert-butyl-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

1-[3-tert-butyl-5-(3-methoxypropoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone,

2-(6-chloro-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone,

1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone,

N,N-diethyl-6-chloro-3-imino-2-{2-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-2-oxoethyl}-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide,

N,N-diethyl-2-[2-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-oxoethyl]-6-chloro-3-imino-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide,

1-[3-tert-butyl-5-(3-methoxypropoxy)phenyl]-2-(6-ethoxy-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone or

1-[3-tert-butyl-5-(2-methoxyethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone.

The expression "$(C_1$-$C_4)$-alkyl" or "$(C_1$-$C_6)$-alkyl" is understood to mean hydrocarbon radicals whose carbon chain is straight-chain or branched and contains from 1 to 4 carbon atoms or from 1 to 6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, 2,3-dimethylbutyl or neohexyl.

The expression "-$(C_0$-$C_4)$-alkylene" or "-$(C_1$-$C_6)$-alkylene" is understood to mean hydrocarbon radicals whose carbon chain is straight-chain or branched and contains 1 to 4 or 1-6 carbon atoms, for example methylene, ethylene, 1-methylmethylene, propylene, 1-

methylethylene, butylene, 1-propylmethylene, 1-ethyl-1-methylmethylene, 1,2-dimethylethylene, 1,1-dimethylmethylene, 1-ethylethylene, 1-methylpropylene, 2-methylpropylene, pentylene, 1-methylbutylene, hexylene, 1-methylpentylene. "-C_0-alkylene" is a covalent bond.

The expression "-O-(C_1-C_6)-alkyl" or "-O-(C_1-C_8)-alkyl" is understood to mean alkoxy radicals whose carbon chain is straight-chain or branched and contains from 1 to 6 or from 1 to 8 carbon atoms, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, 1-pentoxy, 2-pentoxy, 3-pentoxy, 1-hexoxy, 2-hexoxy, 3-hexoxy, 1-heptoxy, 2-heptoxy, 3-heptoxy, 4-heptoxy, 2,4-dimethylpentan-3-oxy, 1-octoxy, 2-octoxy, 3-octoxy, 2,2,4-trimethylpentan-3-oxy, 2,3,4-trimethylpentan-3-oxy or 4-octoxy.

The expression "(C_3-C_6)-cycloalkyl" is understood to mean radicals such as compounds which derive from 3- to 6-membered monocycles such as cyclopropane, cyclobutane, cyclopentane or cyclohexane.

The expression "-O-(C_3-C_6)-cycloalkyl" is understood to mean cycloalkoxy radicals such as compounds which derive from 3- to 6-membered monocycles such as cyclopropoxy, cyclobutoxy, cyclopentoxy or cyclohexoxy.

The expression "-(C_6-C_{14})-aryl" is understood to mean aromatic hydrocarbon radicals having from 6 to 14 carbon atoms in the ring. -(C_6-C_{14})-Aryl radicals are, for example, phenyl, naphthyl, for example 1-naphthyl, 2-naphthyl, anthryl or fluorenyl. Naphthyl radicals and especially phenyl are preferred aryl radicals.

The expression "Het" is understood to mean ring systems having from 4 to 15 carbon atoms which are present in one, two or three ring systems joined to one another and which, according to ring size, may contain one, two, three or four identical or different heteroatoms from the group of oxygen, nitrogen and sulfur. Examples of these ring systems are acridinyl, azepinyl, azetidinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dibenzofuranyl, dibenzothiophenyl, dihydrofuran[2,3-b]-tetrahydrofuranyl, dihydrofuranyl, dioxolyl, dioxanyl, 2H,6H-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl,

isoquinolinyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isothiazolidinyl, 2-isothiazolinyl, isothiazolyl, isoxazolyl, isoxazolidinyl, 2-isoxazolinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2.5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxothiolanyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purynyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridothiophenyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrahydropyridinyl, 6H-1,2.5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2.5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolidinyl, thiazolinyl, thiazolyl, thienyl, thienoimidazolyl, thienooxazolyl, thienopyrrolyl, thienopyridyl, thienothiazolyl, thienothiophenyl, thiomorpholinyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2.5-triazolyl, 1,3,4-triazolyl or xanthenyl radicals.

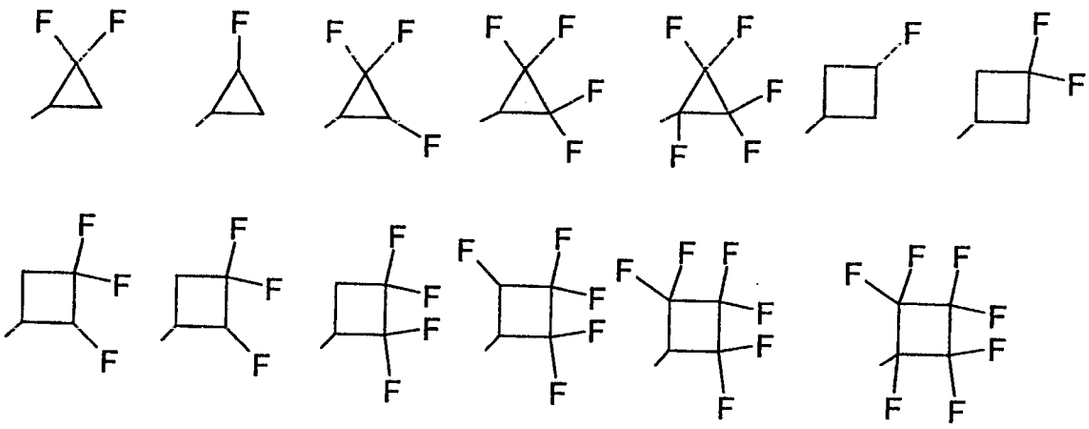
The expression "R1 and R2 or R2 and R3, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of these atoms are replaced by nitrogen, oxygen or sulfur atoms" is understood to mean, for example, ring systems such as 2,3,5,6,7,8-hexahydro-1,2,3a,4,5,8-hexaaza-cyclopenta[b]naphthalene; 2,6,7,8-tetrahydro-3H-5-oxa-1,2,3a,4,8-pentaaza-cyclopenta[b]naphthalene; 2,3,6,7-tetrahydro-5,8-dioxa-1,2,3a,4-tetraaza-cyclopenta[b]naphthalene; 2,3,6,7-tetrahydro-5H-8-oxa-1,2,3a,4,5-pentaaza-cyclopenta[b]naphthalene; 2,6,7,8-tetrahydro-3H-5-thia-1,2,3a,4,8-pentaaza-cyclopenta[b]naphthalene; 2,3,6,7,8,9-hexahydro-1,2,3a,4,6,9-hexaaza-cyclopenta[a]-naphthalene; 2,3-dihydro-5,7-dioxa-1,2,3a,4-tetraaza-s-indacene; 2,6,7,8-tetrahydro-3H-cyclopenta[e][1,2,4]triazolo[4,3-b]pyridazine; 2,7,8,9-tetrahydro-3H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazine or 2,3,6a,9a-tetrahydro-[1,3]dioxolo[4,5-d][1,2,4]-triazolo[4,3-b]pyridazine.

The expression "R4 and R5, R5 and R6, R6 or R7 or R7 and R8, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of these atoms are replaced by nitrogen, oxygen or sulfur atoms" is understood to mean, for example, ring systems such as 2,3-dihydrobenzo[1,4]dioxin; 3,4-dihydro-2H-benzo[1,4]oxazine; 1,2,3,4-tetrahydroquinoxaline; benzo[1,3]dioxole; 3,4-dihydro-2H-benzo[1,4]thiazine or 2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine.

The expressions "R11 and R12 in the "N(R11)-R12" and "N(R11)-C(O)-R12" fragments represent a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-(CO)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S" or "R11 and R12 in the "N(R21)-R22" and "N(R21)-C(O)-R22" fragments is a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-(CO)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S" is understood to mean, for example, ring systems such as cyclic amines such as azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, imidazolyl, morpholinyl or thiomorpholinyl, and in the case of the imides radicals such as pyrrolidine-2,5-dionyl, piperidine-2,6-dionyl, piperazine-2,6-dionyl, morpholine-3,5-dionyl, and in the case of the lactams radicals such as pyrrolidin-2-onyl, piperidin-2-onyl, piperazin-2-onyl, morpholin-3-onyl.

The rearranged expression "alkyl, alkylene or cycloalkyl in which some or all of the hydrogen atoms are replaced by fluorine" is understood to mean a partially fluorinated or perfluorinated alkyl, alkylene or cycloalkyl which derives, for example, for alkyl from the following radicals: $-CF_3$, $-CHF_2$, $-CH_2F$, $-CHF-CF_3$, $-CHF-CHF_2$, $-CHF-CH_2F$, $-CH_2-CF_3$, $-CH_2-CHF_2$, $-CH_2-CH_2F$, $-CF_2-CF_3$, $-CF_2-CHF_2$, $-CF_2-CH_2F$, $-CH_2-CHF-CF_3$, $-CH_2-CHF-CHF_2$, $-CH_2-CHF-CH_2F$, $-CH_2-CH_2-CF_3$, $-CH_2-CH_2-CHF_2$, $-CH_2-CH_2-CH_2F$, $-CH_2-CF_2-CF_3$, $-CH_2-CF_2-CHF_2$, $-CH_2-CF_2-CH_2F$, $-CHF-CHF-CF_3$, $-CHF-CHF-CHF_2$, $-CHF-CHF-CH_2F$, $-CHF-CH_2-CF_3$, $-CHF-CH_2-CHF_2$, $-CHF-CH_2-CH_2F$, $-CHF-CF_2-CF_3$, $-CHF-CF_2-CHF_2$, $-CHF-CF_2-CH_2F$, $-CF_2-CHF-CF_3$, $-CF_2-CHF-CHF_2$, $-CF_2-CHF-CH_2F$, $-CF_2-CH_2-CF_3$, $-CF_2-CH_2-CHF_2$, $-CF_2-CH_2-CH_2F$, $-CF_2-CF_2-CF_3$, $-CF_2-CF_2-CHF_2$, $-CF_2-CF_2-CH_2F$, $-CH(CF_3)_2$, $-CH(CHF_2)_2$, $-CH(CFH_2)_2$, $-CH(CFH_2)(CHF_2)$, $-CH(CFH_2)(CF_3)$, $-CH(CFH_2)(CH_3)$, $-CH(CHF_2)(CH_3)$, $-CH(CF_3)(CH_3)$, $-CF(CF_3)_2$, $-CF(CHF_2)_2$, $-CF(CFH_2)_2$, $-CF(CFH_2)(CHF_2)$, $-CF(CFH_2)(CF_3)$, $-CF(CFH_2)(CH_3)$, $-CF(CHF_2)(CH_3)$, or $-CF(CF_3)(CH_3)$, and also the further possible combinations for butyl, pentyl and hexyl, which, like propyl, may also be branched.

for alkylene, for example, from the following radicals: $-CF_2-$, -CHF-, $-CHF-CF_2-$, $-CHF-CHF-$, $-CHF-CH_2-$, $-CF_2-CF_2-$ or $-CF_2-CH_2F$, and also the further possible combinations for propylene, butylene, pentylene and hexylene, which may also be branched, and for cycloalkyl, for example, from the radicals



and also the analogous larger cyclopentyl and cyclohexyl rings.

The expression "halogen" is understood to mean fluorine, chlorine, bromine or iodine, preference being given to fluorine, chlorine or bromine, especially to fluorine or chlorine.

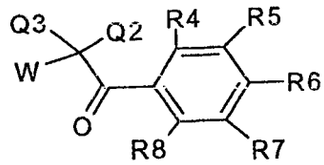
The expressions described above can also be combined as desired, as done, for example, in "-(C_0-C_6)-alkylene-O-(C_0-C_6)-alkylene-(C_6-C_{14})-aryl".

Functional groups of the intermediates used, for example amino or carboxyl groups in the compound of the formula I, may be masked by suitable protecting groups. Suitable protecting groups for amino functions are, for example, the t-butoxycarbonyl, the benzyloxycarbonyl or the phthaloyl group, and also the trityl or tosyl protecting group. Suitable protecting groups for the carboxyl function are, for example, alkyl, aryl or arylalkyl esters. Protecting groups can be introduced and removed by techniques which are well known or are described here (see Greene, T. W., Wuts, P. G. M., Protective Groups in Organic Synthesis (1999), 3rd Ed., Wiley-Interscience, or Kocienski, P. J., Protecting Groups (2004), 3rd Ed., Thieme. The expression "protecting group" may also include corresponding polymer-bound protecting groups.

The inventive compounds can be prepared by well-known processes or by processes described here.

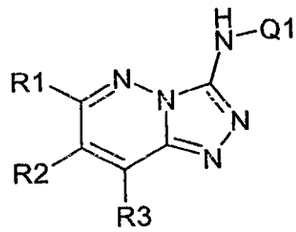
The invention further relates to a process for preparing the compound of the formula I and/or a stereoisomeric form of the compound of the formula I and/or a physiologically compatible salt of the compound of the formula I, which comprises

a) reacting a compound of the formula II



(II)

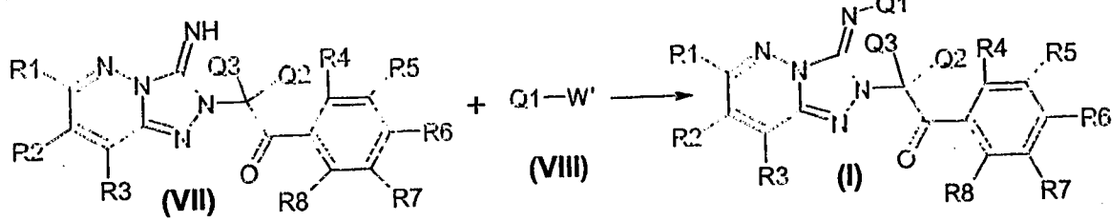
where R4, R5, R6, R7, R8, Q2 and Q3 are each as defined in formula I and W is chloride, bromide, mesylate or tosylate with a compound of the formula III



(III)

where R1, R2, R3 and Q1 are each as defined in formula I, with or without addition of base, in a solvent to give a compound of the formula I, or

b) reacting a compound of the formula VII



where R1, R2, R3, R4, R5, R6, R7, R8, Q1, Q2 and Q3 are each as defined in formula I with a compound Q-W' where W' is chloride, bromide, mesylate, tosylate, methylsulfate or a similar good leaving group, with or without addition of base, to give a compound of the formula I, or

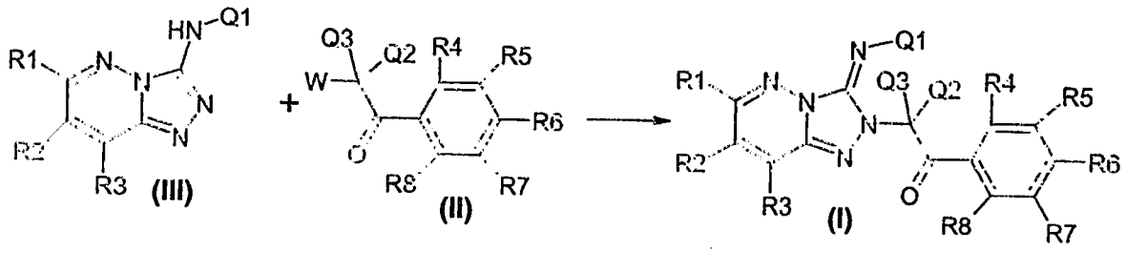
c) either isolating the compound of the formula I prepared by method a) or b) in free form or releasing it from physiologically incompatible salts or, in the case of the presence of acidic or basic groups, converting it to physiologically compatible salts, or

d) separating a compound of the formula I prepared by method a) or b), or a suitable precursor of the formula I which, owing to its chemical structure, occurs in enantiomeric or diastereomeric forms, into the pure enantiomers or diastereomers by

salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and elimination of the chiral auxiliary groups.

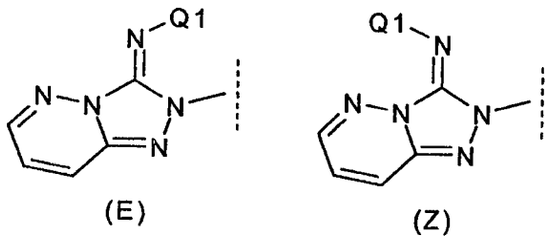
The invention further relates to a process for preparing the compound of the formula I according to scheme 1.

Scheme 1:

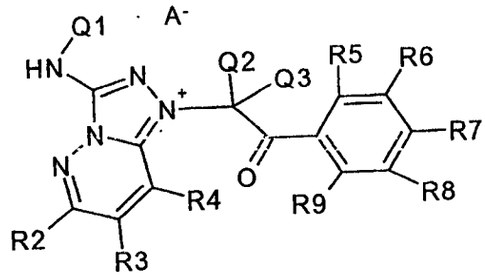


The reactants II and III, III optionally being present in the form of a salt, are converted at room temperature or a slightly elevated temperature from 40°C to 60°C, advantageously, when III is in the form of a salt, in the presence of a base, preferably Hünig's base, in a solvent, preferably dimethylformamide (DMF) or dioxane, to give the compound of the formula I. The R1, R2, R3, R4, R5, R6, R7, R8, Q1, Q2 and Q3 radicals are each as defined in formula I, W represents a good leaving group such as chloride, bromide, mesylate or tosylate, preferably bromide or mesylate.

Some of the compounds of the formula I may also occur in isomeric forms, in which case Q1 in the following subformula of formula I may have either (E) or (Z) configuration:

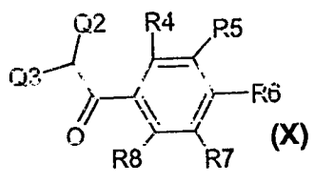


The 1-substituted triazolopyridazinium salts (A) which are likewise formed in different proportions under these reaction conditions according to the substitution pattern can be removed by chromatography or by crystallization. It is advantageous to separate by means of silica gel with dichloromethane-methanol as the eluent mixture.

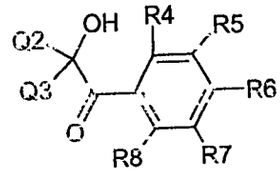


(A)

Compounds of the formula II can be obtained commercially or by literature methods, for example proceeding from the corresponding acetophenones X or X' (see, for example: Phosphorus and Sulfur and the Related Elements (1985), 25(3), 357 or Tetrahedron Letters (1984), 25(34), 3715). The well-known compounds of the X type can, for example, be functionalized on the acetyl group with, among other reagents, elemental bromine or chlorine, tribromide derivatives such as phenyltrimethylammonium tribromide, 1,3-dichlorodimethylhydantoin, N-chloro- or N-bromosuccinimide. Compounds of the X' type can be converted, for example, using mesyl or tosyl chloride to the compounds of the II type.

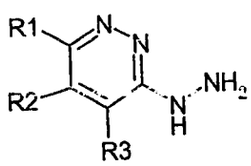


(X)

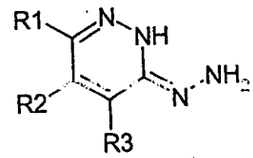


(X')

Compounds of the formula III can be obtained commercially or by literature methods. Suitable precursors are compounds of the XX type, which can be cyclized in the presence of cyanogen bromide, cyanogen chloride or tosyl cyanide to give compounds of the III type, and which may also be present in the tautomeric form of the XXa type.



(XX)

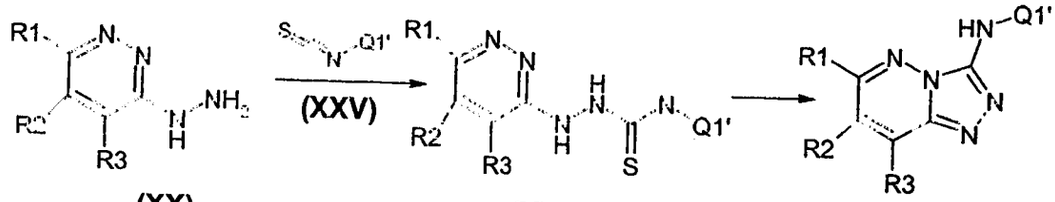


(XXa)

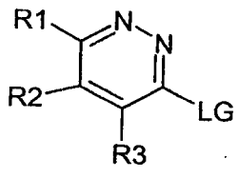
The compound of the formula XX such as pyridazin-3-ylhydrazine and the compound of the formula XXa such as [2H-pyridazin-(3E)-ylidene]hydrazine are tautomeric forms. When only one notation is utilized hereinafter, this means that the other tautomeric form is also disclosed.

Alternatively, compounds of the XX type can also be reacted with isothiocyanates of the XXV type to given the thioureas of the XXVI type. The latter can, after activation of the sulfur, for example with tosyl chloride, a carbodiimide, ethyl bromoacetate or mercury oxide,

be converted to the compounds of the formula III type. The R1, R2 and R3 radicals here are each as defined above and Q1' corresponds to Q1 or a protecting group such as FMOC (fluoren-9-ylmethyloxycarbonyl), which, after ring closure, can be eliminated again, and so compounds where Q1 is hydrogen are obtainable.

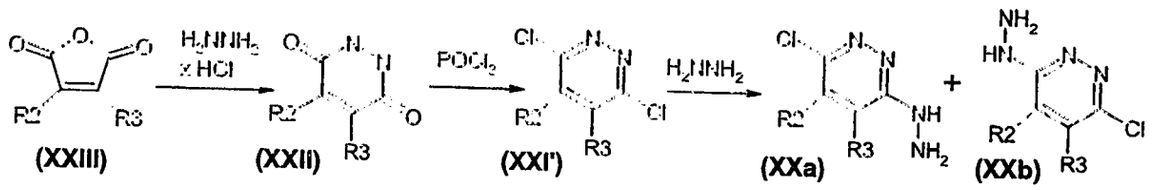


Compounds of the XX type can be obtained by incorporating hydrazine into compounds of the XXI type, which are commercially available with a wide variety of different substitution patterns. The R1, R2 and R3 radicals here are each as defined above and LG represents a good leaving group such as fluorine, chlorine, bromine, iodine, mesylate, tosylate, triflate or nonaflate.



(XXI)

One route to the chlorine compounds of the XXI' type is, for example, the reaction of maleic anhydrides of the XXIII type with hydrazine hydrochloride to give the compounds of the XXII type, followed by the reaction with phosphorus oxychloride to give the dichloride XXI' and with hydrazine to give the compounds of the XXa and XXb type.



A compound of the formula I prepared according to scheme 1, or a suitable precursor of the formula I which, owing to its chemical structure, occurs in enantiomeric forms, can be separated into the pure enantiomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and elimination of the chiral auxiliary groups (process e), or the compound of the formula I prepared according to scheme 1 can either be isolated in free form or, in the case of

the presence of acidic or basic groups, converted to physiologically compatible salts (process d).

Acidic or basic products of the compound of the formula I may be in the form of their salts or in free form. Pharmacologically acceptable salts are preferred, for example alkali metal or alkaline earth metal salts or hydrochlorides, sulfates, hemisulfates, methylsulfonates, p-toluenesulfonates, all possible phosphates, and salts of amino acids, natural bases or carboxylic acids such as lactates, citrates, tartrates, acetates, adipates, fumarates, gluconates, glutamates, maleates or pamoates.

Physiologically tolerated salts are prepared from compounds of the formula I capable of salt formation, including their stereoisomeric forms, in process step c) in a manner known per se. If compounds of the formula I contain acidic functionality, stable alkali metal, alkaline earth metal or optionally substituted ammonium salts can be formed with basic reagents such as hydroxides, carbonates, bicarbonates, alkoxides, and ammonia or organic bases, for example trimethyl- or triethylamine, ethanolamine, diethanolamine or triethanolamine, trometamol or else basic amino acids, for instance lysine, ornithine or arginine. Basic groups of the compounds of the formula I form acid addition salts with acids. Suitable for this purpose are both inorganic and organic acids such as hydrochloric or hydrobromic, sulfuric, hemisulfuric, phosphoric, methanesulfonic, benzenesulfonic, p-toluenesulfonic, 4-bromobenzenesulfonic, cyclohexylamidosulfonic, trifluoromethylsulfonic, 2-hydroxyethanesulfonic, acetic, oxalic, tartaric, succinic, glycerolphosphoric, lactic, malic, adipic, citric, fumaric, maleic, gluconic, glucuronic, palmitic or trifluoroacetic acid.

In process step d), the compound of the formula I, if it occurs as a mixture of diastereomers or enantiomers or results as mixtures thereof in the chosen synthesis, is separated into the pure stereoisomers either by chromatography on an optionally chiral support material or, if the racemic compound of the formula I is capable of salt formation, it is also possible to carry out a fractional crystallization of the diastereomeric salts formed with an optically active base or acid as auxiliary. Examples of suitable chiral stationary phases for thin-layer or column chromatographic separation of enantiomers are modified silica gel supports (called Pirkle phases) and high molecular weight carbohydrates such as triacetylcellulose. For analytical purposes it is also possible to use gas chromatographic methods on chiral stationary phases after appropriate derivatization known to the skilled worker. To separate enantiomers of the

racemic carboxylic acids, the diastereomeric salts of differing solubility are formed with an optically active, usually commercially available, base such as (-)-nicotine, (+)- and (-)-phenylethylamine, quinine bases, L-lysine or L- and D-arginine, the less soluble component is isolated as solid, the more soluble diastereomer is deposited from the mother liquor, and the pure enantiomers are obtained from the diastereomeric salts obtained in this way. It is possible in the same way in principle to convert the racemic compounds of the formula I which contain a basic group such an amino group, with optically active acids such as (+)-camphor-10-sulfonic acid, D- and L-tartaric acid, D- and L-lactic acid, and (+) and (-)-mandelic acid, into the pure enantiomers. It is also possible to convert chiral compounds containing alcohol or amine functions with appropriately activated or, where appropriate, N-protected enantiopure amino acids into the corresponding esters or amides, or conversely chiral carboxylic acids with carboxy-protected enantiopure amino acids into the amides or with enantiopure hydroxy carboxylic acids such as lactic acid into the corresponding chiral esters. The chirality of the amino acid or alcohol residue which has been introduced in enantiopure form can then be utilized to separate the isomers by carrying out a separation of the diastereomers which are now available by crystallization or chromatography on suitable stationary phases, and then eliminating the included chiral moiety again by suitable methods. A further possibility with some of the inventive compounds is to prepare the framework structures using diastereomerically or enantiomerically pure starting materials. It is thus possible also to employ other or simplified processes for purifying the final products. These starting materials have previously been prepared enantiomerically or diastereomerically pure by processes known from the literature. This may mean in particular that either enantioselective processes are employed in the synthesis of the basic structures, or else a separation of enantiomers (or diastereomers) is carried out at an early stage of the synthesis and not at the stage of the final products. A simplification of these separations can likewise be achieved by proceeding in two or more stages.

The invention also relates to medicaments having an effective content of at least one compound of the formula I and/or a physiologically tolerated salt of the compound of the formula I and/or an optionally stereoisomeric form of the compound of the formula I, together with a pharmaceutically suitable and physiologically tolerated carrier, additive and/or other active ingredients and excipients.

Owing to the pharmacological properties, the compounds of the invention are suitable for example for the prophylaxis, secondary prevention and therapy of all disorders which can be treated by inhibition of the protease-activated receptor 1 (PAR1). Thus, the compounds of the invention are suitable both for a prophylactic and a therapeutic use on humans. They are suitable both for acute treatment and for long-term therapy. The compounds of the formula I can be employed in patients suffering from impairments of well being or diseases associated with thromboses, embolisms, hypercoagulability, fibrotic changes or inflammatory disorders. These include myocardial infarction, angina pectoris and all other types of acute coronary syndrome, stroke, peripheral vascular disorders, deep vein thrombosis, pulmonary embolism, embolic or thrombotic events caused by cardiac arrhythmias, cardiovascular events such as restenosis following revascularization, angioplasty and similar procedures such as stent implantations and bypass operations. The compounds of the formula I can further be employed in all procedures leading to contact of blood with foreign surfaces, such as for dialysis patients and patients with indwelling catheters. Compounds of the formula I can be employed in order to reduce the risk of thrombosis following surgical procedures such as knee and hip joint operations.

Compounds of the formula I are suitable for the treatment of patients with disseminated intravascular coagulation, sepsis and other intravascular events associated with inflammation. The compounds of the formula I are further suitable for the prophylaxis and treatment of patients with atherosclerosis, diabetes and the metabolic syndrome and the sequelae thereof. Impairments of the hemostatic system (for example fibrin deposits) have been implicated in mechanisms leading to tumor growth and tumor metastasis, and in inflammatory and degenerative articular disorders such as rheumatoid arthritis and arthrosis. Compounds of the formula I are suitable for retarding or preventing such processes.

Further indications for the use of the compounds of the formula I are fibrotic changes in the lung such as chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS) and of the eye such as fibrin deposits following eye operations. Compounds of the formula I are also suitable for the prevention and/or treatment of scarring.

The medicaments of the invention can be administered by oral, inhalational, rectal or transdermal administration or by subcutaneous, intraarticular, intraperitoneal or intravenous

injection. Oral administration is preferred. Coating of stents with compounds of the formula I and other surfaces which come into contact with blood in the body is possible. The invention also relates to a process for manufacturing a medicament, which comprises making a suitable dosage form from at least one compound of the formula I with a pharmaceutically suitable and physiologically tolerated carrier and, where appropriate, further suitable active ingredients, additives or excipients.

Suitable solid or pharmaceutical formulations are, for example, granules, powder, coated tablets, tablets, (micro)capsules, suppositories, syrups, solutions, suspensions, emulsions, drops or injectable solutions, and products with protracted release of active ingredient, in the production of which customary aids such as carriers, disintegrants, binders, coating agents, swelling agents, glidants or lubricants, flavorings, sweeteners and solubilizers are used. Excipients which are frequently used and which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, cellulose and its derivatives, animal and vegetable oils such as fish liver oil, sunflower, peanut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and monohydric or polyhydric alcohols such as glycerol.

The pharmaceutical products are preferably manufactured and administered in dosage units, where each unit comprises as active ingredient a particular dose of the compound of the invention of the formula I. In the case of solid dosage units such as tablets, capsules, coated tablets or suppositories, this dose can be up to about 1000 mg, but preferably about 50 to 300 mg and, in the case of injection solutions in ampoule form, up to about 300 mg but preferably about 10 to 100 mg.

The daily doses indicated for the treatment of an adult patient weighing about 70 kg are, depending on the activity of the compound of formula I, from about 2 mg to 1000 mg of active ingredient, preferably about 50 mg to 500 mg. However, in some circumstances, higher or lower daily doses may also be appropriate. The daily dose can be administered either by a single administration in the form of a single dosage unit or else a plurality of smaller dosage units or by multiple administration of divided doses at particular intervals.

Compounds of the formula I can be administered both as monotherapy and in combination or together with all antithrombotics (anticoagulants and platelet aggregation inhibitors), thrombolytics (plasminogen activators of every type), other substances having profibrinolytic activity, antihypertensives, regulators of blood glucose, lipid-lowering agents and

antiarrhythmics. Suitable platelet aggregation inhibitors in this connection are cyclooxygenase 1 inhibitors such as aspirin, irreversible $P2Y_{12}$ antagonists such as clopidogrel or prasugrel, reversible $P2Y_{12}$ antagonists such as cangrelor or AZD6140 and thromboxane A_2/prostaglandin H_2 antagonists such as terutroban. It has been possible to show additive effects of PAR1 blockade in combination with $P2Y_{12}$ blockade for example (Eur. Heart J. 2007, 28, Abstract Supplement, 188).

Examples

End products were generally characterized by a chromatographic method with ultraviolet and mass spectrometry detection (LCUV/ESI-MS coupling), and ^{1}H NMR. The compounds are described by reporting the corresponding retention time in the ion current (LC-MS rt) and the corresponding $[M+H]^+$ signal in the case of positive ionization in the corresponding mass spectrum. When no $[M+H]^+$ mass signal could be obtained, the ^{1}H NMR data were reported as an alternative. Abbreviations used are either explained or correspond to the usual conventions.

Silica gel separations were carried out manually (flash chromatography) or supported by semiautomatic cartridge systems such as Companion (CombiFlash) or Flashmaster II (Jones Chromatography). Unless stated otherwise, chromatographic separations were carried out on silica gel with ethyl acetate/heptane, dichloromethane/ethanol or dichloromethane/methanol mixtures as the eluent.

Solvents were evaporated generally under reduced pressure at from 35°C to 45°C on a rotary evaporator, which is referred to by phrases such as "concentrated", "concentrated by rotary evaporation", "dried", "freed of the solvent", "solvent removed or drawn off" or similar expressions.

The LCUV/MS analyses were carried out under the following conditions:

Method A (=met. a):

System:	Agilent 1100 HPLC-System coupled to 1100 LC/MSD
Column:	YMC J'shere ODS HS0 20x2.1 mm, packing material 4 µm
Eluent:	ACN:H_2O+0.05% TFA (flow rate 1 ml/min)

Gradient: 4:96 (0 min) → 95:5 (2 min) → 95:5 (2.4 min) →4:96 (2.45 min)

Ionization: ESI^+

Method B (=met. b):

System: Agilent 1200 HPLC-System coupled to 6120 LC/MS

Column: Luna C18, 10 x 2.0 mm, packing material 3 µm

Eluent: ACN:H_2O+0.05% TFA (flow rate 1.1 ml/min)

Gradient: 7:93 (0 min) → 95:5 (1 min) → 95:5 (1.45 min) → 7:93 (1.5 min)

Ionization: ESI^+

Method C (=met. c):

System: Agilent 1200 HPLC-System coupled to 6120 LC/MS

Column: Luna C18, 10 x 2.0 mm, packing material 3 µm

Eluent: ACN:H_2O+0.05% TFA (flow rate 1.1 ml/min)

Gradient: 1:99 (0 min) → 7:93 (0.3 min) → 95:5 (1.3 min) →95:5 (1.75 min) → 1:99 (1.8 min)

Ionization: ESI^+

Method D (=met. d):

System: Waters: 1525 pump, 996 PDA, LCT classic TOF-MS

Column: Waters XBridge C18 4.6 x 50 mm; 2.5 µM

Eluent: ACN+0.05 % TFA : H_2O+0.05 % TFA (flow rate 1.3 ml/min), 40°C

Gradient: 5:95 (0 min) → 5:95 (0.3 min) → 95:5 (3.5 min) →95:5 (4 min)

Ionization: ESI^+

Method E (=met. e):

System: Waters: 1525 pump, 996 PDA, LCT classic TOF-MS

Column: Waters XBridge C18; 4.6 x 50 mm; 2.5 µM

Eluent: ACN+0.05 % TFA : H_2O+0.05 % TFA (flow rate 1.7 ml/min), 40°C

Gradient: 5:95 (0 min) → 5:95 (0.2 min) → 95:5 (2.4 min) → 95:5 (3.2 min) → 5:95 (3.3 min) → 5:95 (4.0 min)

Ionization: ESI^+

Method F (=met. f):

System:	Waters: 1525 pump, 996 PDA, LCT classic TOF-MS
Column:	YMC J'shere, 33 x 2 mm, 4 µM
Eluent:	ACN+0.05 % TFA : H_2O+0.05 % TFA (flow rate 1.3 ml/min)
Gradient:	5:95 (0 min) → 5:95 (2.5 min) → 95:5 (3 min)
Ionization:	ESI^+

Preparative HPLC purifications on reversed-phase (RP) silica gel were carried out by the following methods:

Method A (=met. A):

Column:	Merck (Darmstadt, Deutschland) Purosphere® RP18 25x250 mm, 10 µm
Eluent:	ACN:H_2O+0.05%TFA (flow rate 25 ml/min)
Gradient:	10:90 (0 min) → 90:10 (40 min)

Method B (=met. B)

Column:	Merck Purosphere® RP18 25x250 mm, 10 µm
Eluent:	ACN:H_2O+0.05%TFA (flow rate 25 ml/min)
Gradient:	0:100 (0 min) → 0:100 (5 min) → 20:80 (20 min)

Method C (=met. C)

Column:	Agilent Prep-C18, 30 x 250mm, 10 µm
Eluent:	ACN:H_2O+0.05%TFA (flow rate 75 ml/min)
Gradient:	10:90 (0 min) → 90:10 (12.5 min) → 90:10 (15min) →10:90 (15.5 min) →10:90 (17.5 min)

Method D (=met. D):

Column:	Merck (Darmstadt, Deutschland) Purosphere® RP18 25x250 mm, 10 µm
Eluent:	ACN:H_2O+0.05% conc. HCl (flow rate 25 ml/min)
Gradient:	10:90 (0 min) → 90:10 (40 min)

Method E (=met. E)

Column:	Merck Purosphere® RP18 25x250 mm, 10 µm
Eluent:	ACN:H_2O+0.05%HCl (flow rate 25 ml/min)
Gradient:	0:100 (0 min) → 0:100 (5 min) → 20:80 (20 min)

Method F (=met. F)

Column:	Agilent Prep-C18, 30 x 250mm, 10 µm
Eluent:	ACN:H_2O+0.05%TFA (flow rate 75 ml/min)
Gradient:	0:100 (0 min) → 0:100 (5 min) → 20:80 (20min)

The reactions took place in standard reaction apparatus such as single-neck or multineck flasks, which, unless stated otherwise, according to the need, had a capacity of from 5 ml to 2000 ml and, as required, were equipped with a septum, stopper, condenser, stirrer or other equipment. Unless mentioned otherwise, all reactions took place under argon as protective gas and were stirred with magnetic stirrers. Microwave reactions were carried out in the Emrys Optimizer from Personal Chemistry in vessels of capacity from 0.5 ml to 10 ml according to the need.

Solvents such as dichloromethane, ethanol, dimethylformamide, methanol, isopropanol and the like were purchased as "dry" solvents and were also used thus in the reactions, without this being explicitly mentioned in each case.

Abbreviations used:

abs.	absolute
ACN	acetonitrile
Boc	butoxycarbonyl
Ex. example	
DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine (Hünig's base)
DMF	dimethylformamide

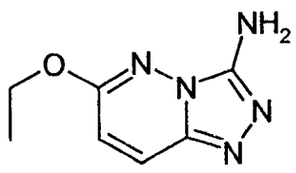
DMSO	dimethyl sulfoxide
EA	ethyl acetate
eq.	equivalents
EtOH	ethanol
h	hour(s)
HPLC	high-performance liquid chromatography
Hünig's base	N,N-diisopropyl-N-ethylamine
LC-MS rt	retention time of the compound in the ion current of liquid chromatography
LCUV/MS	ultraviolet liquid chromatography/mass spectrometry
NMP	1-methyl-2-pyrrolidone
MeOH	methanol
MtB ether	*tert*-butyl methyl ether
MW	microwave
RF	reflux
RT	room temperature (20°C to 25°C)
rt	retention time
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TOTU	O-[(ethoxycarbonyl)cyanomethyleneamino]-N,N,N',N'-tetramethyl-uronium tetrafluoroborate

Synthesis of the units of the "western half":

W1

W1.001

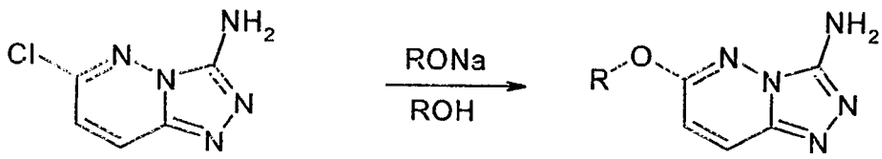
6-Ethoxy-[1,2,4]triazolo[4,3-b]-pyridazin-3-ylamine



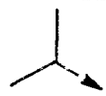
6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.001a, 616 mg) was dissolved in absolute ethanol (40 ml) and admixed with portions of solid sodium ethoxide (990 mg). After stirring at 55°C for 2 h, water was added and the aqueous phase was extracted three times with dichloromethane. The combined extracts were dried over sodium sulfate, filtered and concentrated. 709 mg of crude product of the desired compound were obtained in sufficient purity.

LC-MS rt: 0.51 min $[M+H]^+$: 180.1 (met. a)

The following were synthesized analogously:

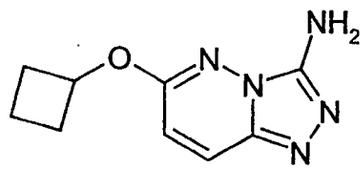


W2.001a

Number	R	LC-MS rt	$[M+H]^+$	Comment:
W1.002	methyl-	0.22	166.1 (met. a)	W2.001a (100 mg); sodium methoxide solution; product: 95 mg
W1.003		0.69	194.1 (met. a)	W2.001a (100 mg); sodium isopropoxide solution; product: 84 mg

W1.004

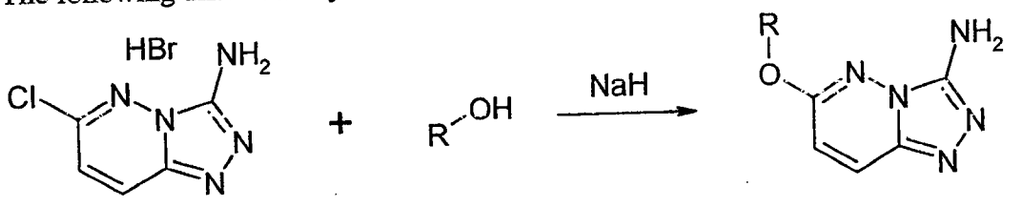
6-Cyclobutoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



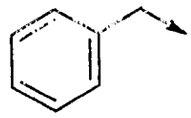
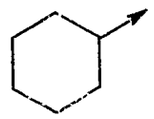
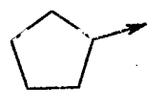
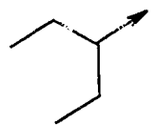
Cyclobutanol (2.43 ml) was initially charged at RT with stirring and cooled almost to 0°C with an ice bath. Subsequently, the mixture was admixed with portions of sodium hydride (146 mg). The suspension formed was heated to 55°C for 30 min and admixed with portions of 6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.001, 200 mg), suspended in cyclobutanol (5 ml). After stirring at 55°C for 1.5h, the mixture was left to stand at RT overnight and then admixed with water and extracted three times with

dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 136 mg of the title compound were obtained in solid form. LC-MS rt: 0.82 min $[M+H]^+$: 206.2 (met. a)

The following units were synthesized analogously:

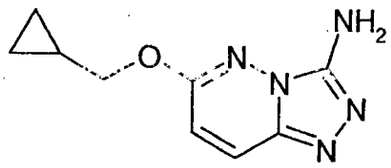


W2.001

Number	R	LC-MS rt	$[M+H]^+$	Comment:
W1.005		0.89 min	242.1 (met. a)	W2.001a (100 mg) used dissolved in NMP; crude product purified by chromatography using silica gel with dichloromethane/methanol gradient; product: 48 mg
W1.006		0.95 min	234.1 (met. a)	W2.001 (200 mg); Crude product purified by preparative HPLC (met. A); product: 47 mg (TFA salt)
W1.007		0.88 min	220.1 (met. a)	W2.001 (463 mg); Crude product purified by preparative HPLC (met. A); product: 15 mg (TFA salt)
W1.008		0.92 min	222.1 (met. a)	W2.001a (194 mg) used suspended in a mixture of 10 ml of DMF and 5 ml of 3-pentanol; crude product purified by chromatography using silica gel with dichloromethane/methanol gradient; product: 155 mg

W1.009

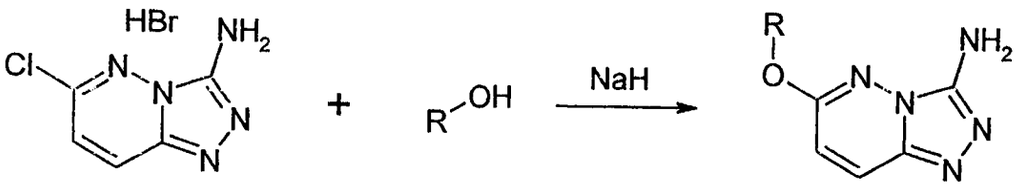
6-Cyclopropylmethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



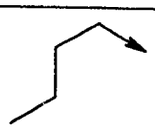
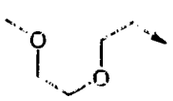
Cyclopropylmethanol (2.64 ml) was initially charged in DMF (35 ml), admixed under argon with sodium hydride (795 mg) and stirred at 40°C for 1 h. Subsequently, 6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.001; 1.66 g), dissolved in DMF (35 ml), were added dropwise. After 1 h, the mixture was admixed with water and extracted by shaking four times with dichloromethane. The combined organic phases were dried over magnesium sulfate and concentrated by rotary evaporation. The residue was triturated with MtB ether, filtered off with suction and dried. 720 mg of the title compound were obtained.

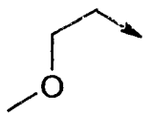
LC-MS rt: 0.80 min $[M+H]^+$: 206.1 (met. f)

The following units were synthesized analogously:



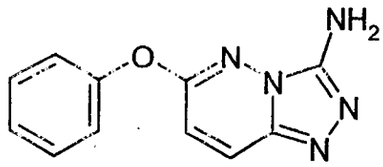
W2.001

Number	R	LC-MS rt [min]	$[M+H]^+$	Comment:
W1.010		0.91	208.2 (met. a)	W2.001 (1.75 g); stirred at 45°C for 1.5 h; product: 820 mg
W1.011		0.63	254.1 (met. a)	W2.001 (2.5 g); crude product purified by means of a silica gel cartridge (120 g, gradient; 0-20 % dichloromethane/methanol in 60 min); product: 1.08 g

W1.012		0.52	210.1 (met. a)	W2.001 (2.5 g); crude product purified by means of a silica gel cartridge (40 g, gradient; 0-20 % dichloromethane/methanol in 60 min); product: 1.04 g

W1.013

6-Phenoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

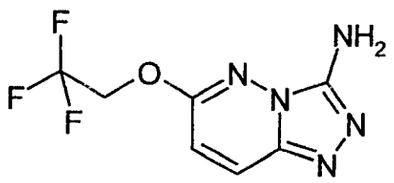


6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.001; 200 mg) were initially charged dissolved in NMP (4 ml). Thereafter, sodium phenoxide (185 mg) was introduced at RT. After stirring at RT for one hour, the reaction was completed by heating to 55°C for 2 h. Subsequently, the mixture was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. The crude product was purified using silica gel with a dichloromethane/methanol gradient. 38 mg of the title compound were obtained in solid form.

LC-MS rt: 0.80 min $[M+H]^+$: 228.1 (met. a)

W1.014

6-(2,2,2-Trifluoroethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

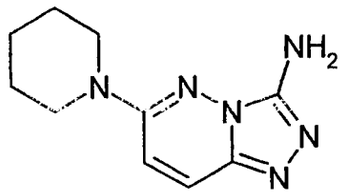


2,2,2-Trifluoroethanol (1 ml), sodium hydride (86 mg) and 6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.001, 100 mg) were reacted according to W1.004. 87 mg of the title compound were obtained in solid form.

LC-MS rt: 0.68 min $[M+H]^+$: 234.1 (met. a)

W1.020

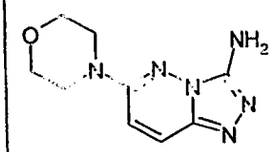
6-Piperidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.001; 100 mg) were initially charged in water (1 ml) and admixed with piperidine (260 µl) with stirring. Thereafter, the mixture was heated to reflux for 1 h and. after cooling, freed of the solvent. Subsequently, the mixture was admixed with water and the solid formed was filtered off with suction and dried. The mother liquor was dried and admixed with a little water. The solid obtained was filtered off with suction and dried. The filtrate was then extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. The three resulting solid fractions were combined and gave rise to 56 mg of the title compound.

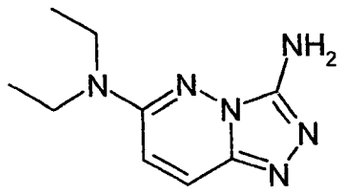
LC-MS rt: 0.77 min $[M+H]^+$: 219.1 (met. a)

The following was prepared analogously:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.021		0.55 min	221.1 (met. a)	W2.001 (150 mg); reflux for 5 h; dry crude product admixed with water and extracted directly with DCM. product: 81 mg

W1.022

N*6*,N*6*-Diethyl-[1,2,4]triazolo[4,3-b]pyridazine-3,6-diamine



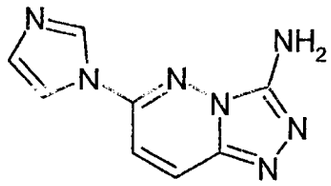
6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.001; 150 mg) was

initially charged in water (5 ml) and admixed with diethylamine (814 µl) while stirring. Thereafter, the mixture was heated to reflux for 16 h and then further diethylamine (407 µl) was added. After refluxing for a further 12 h, the mixture was freed of the solvent, admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 67 mg of the title compound were obtained.

LC-MS rt: 0.72 min $[M+H]^+$: 207.1 (met. a)

W1.023

6-Imidazol-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

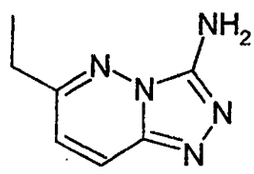


(6-Imidazol-1-ylpyridazin-3-yl)hydrazine (500 mg) were initially charged in a mixture of acetic acid (4 ml) and water (8 ml) with addition of sodium acetate (232 mg) at RT while stirring. Thereafter, the mixture was cooled to 0°C and cyanogen bromide (330 mg) was introduced in portions. After stirring for 2.5 h, the mixture was left to stand overnight. After cooling to 0°C, the mixture was alkalized with 10 M sodium hydroxide solution and extracted repeatedly with EA. The combined EA phases were dried over sodium sulfate, filtered and concentrated. 66 mg of the title compound were isolated.

Further product was still present in the aqueous phase, which was freeze-dried and left to stand. LC-MS rt: 1.46 min $[M+H]^+$: 202.1 (met. d)

W1.025

6-Ethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



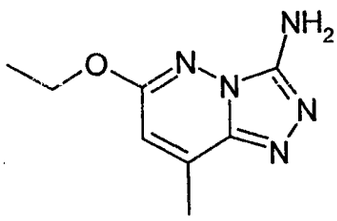
(6-Ethylpyridazin-3-yl)hydrazine hydrochloride (2 g) was initially charged in a mixture of ethanol (30 ml) and water (6 ml) while stirring at RT. Thereafter, cyanogen bromide was

cautiously added dropwise (2.4 g dissolved in 7.5 ml of ethanol and 1.5 ml of water). After stirring at RT for one hour, the mixture was left to stand overnight and, the next day, stirred for 4 further hours. The solvent was then drawn off and the residue was purified by means of preparative HPLC (met. C). The clean product fractions were combined, freed of the acetonitrile under reduced pressure, alkalized with saturated potassium carbonate solution and extracted repeatedly with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. 830 mg of the title compound were obtained. The aqueous potassium carbonate phase was likewise freeze-dried, then taken up with a little water and extracted five times with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. A further 180 mg of the title compound were obtained.

LC-MS rt: 0.32 min $[M+H]^+$: 164.1 (met. a)

W1.030

6-Ethoxy-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine trifluoroacetate (W2.002b; 50 mg) was dissolved in ethanol (3.5 ml) while stirring at RT. Thereafter, sodium ethoxide was added dropwise while cooling with ice (25 mg dissolved in 1.5 ml of ethanol). After stirring at RT for 2.5 h, the mixture was heated to 60°C and, after 2.5 h, a further equivalent of sodium ethoxide solution was added. After standing overnight, the mixture was heated again to 60°C, two further equivalents of sodium ethoxide solution were added and the mixture was stirred for 4 h. Subsequently, the mixture was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 27 mg of the title compound were obtained. LC-MS rt: 0.67 min $[M+H]^+$: 194.1 (met. a)

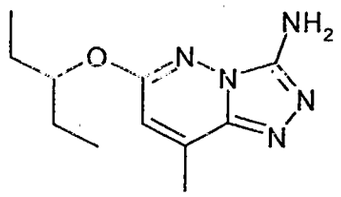
Alternative:

6-Chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.002; 2.5 g) were dissolved in ethanol (50 ml), admixed under argon with sodium ethoxide (3.86 g) and stirred at 60°C for 1 h. Then the mixture was dried and the residue was purified using a 40 g silica gel cartridge (0-20 % dichloromethane-ethanol gradient in 40 min). The clean product fractions were combined and dried. 1.76 g of the title compound were obtained.

LC-MS rt: 1.48 min $[M+H]^+$: 194.1 (met. e)

W1.031

6-(1-Ethylpropoxy)-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

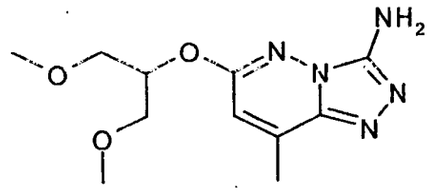


3-Pentanol (10.2 ml) was initially charged at RT with stirring and cooled almost to 0°C with an ice bath. Subsequently, the mixture was admixed with portions of sodium hydride (511 mg). The suspension formed was heated to 55°C for 30 min and admixed with portions of 6-chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine trifluoroacetate (W2.002b; 500 mg), suspended in 3-pentanol (5 ml) and DMF (10 ml). After stirring at 55°C for 1.5 h, the mixture was left to stand at RT overnight, the DMF was removed under reduced pressure, and the residue was then admixed with water and extracted four times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. The residue was purified by means of preparative HPLC (met. A), and the clean product fractions were combined, freed of the acetonitrile under reduced pressure, alkalized with saturated potassium carbonate solution and extracted repeatedly with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. 198 mg of the title compound were obtained.

LC-MS rt: 1.24 min $[M+H]^+$: 236.2 (met. a)

W1.032

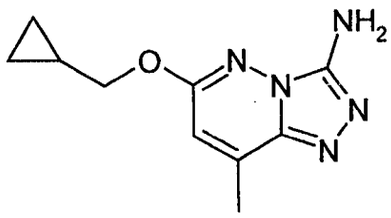
6-(2-Methoxy-1-methoxymethylethoxy)-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



1,3-Dimethoxypropan-2-ol (12.96 ml) was initially charged in DMF (25 ml), admixed under argon with sodium hydride (681 mg) and stirred at 40°C for 1 h. Subsequently, 6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.002; 1.5 g), dissolved in DMF (25 ml), was added dropwise within 20 min. After 1 h, the mixture was admixed with water and extracted by shaking four times with dichloromethane. The combined organic phases were dried over magnesium sulfate and concentrated by rotary evaporation. The residue was triturated with MtB ether, filtered off with suction and dried. 764 mg of the title compound were isolated. LC-MS rt: 0.74 min $[M+H]^+$: 268.1 (met. a)

W1.033

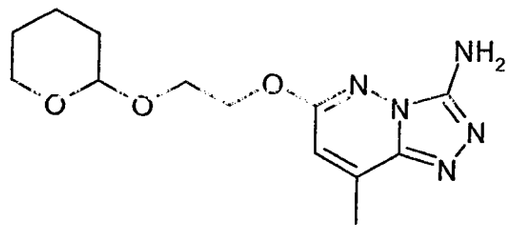
6-Cyclopropylmethoxy-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



Cyclopropylmethanol (2.99 ml) was initially charged in DMF (30 ml), admixed under argon with sodium hydride (907 mg) and stirred at 50°C for 1 h. Subsequently, 6-chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.002; 2.0 g) were dissolved in DMF (30 ml) and one equivalent of the alkoxide solution was added. After stirring at 50°C for one hour, two further equivalents of alkoxide solution were added and the mixture was stirred further at 50°C. The reaction mixture was then dried and purified using silica gel (80 g cartridge, dichloromethane/methanol gradient of 0-10% in 40 min). 620 mg of the title compound were obtained. LC-MS rt: 0.57 min $[M+H]^+$: 220.1 (met. b)

W1.034

8-Methyl-6-[2-(tetrahydropyran-2-yloxy)ethoxy]-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

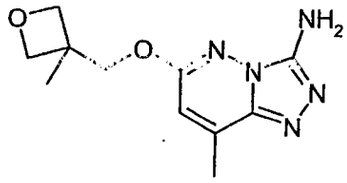


2-(Tetrahydropyran-2-yloxy)ethanol (3.55 ml) was initially charged in DMF (25 ml), admixed under argon with sodium hydride (681 mg) and stirred at 40°C for 0.5 h. Subsequently, 6-chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.002; 1.5 g), dissolved in DMF (25 ml), was added dropwise. After 40 min, the mixture was admixed with water and extracted by shaking four times with dichloromethane. To eliminate the excess alcohol, the mixture was chromatographed first through a short silica gel column with MtB ether and then with 8:2 dichloromethane/methanol. The clean product fractions were combined and dried. 678 mg of the title compound were obtained.

LC-MS rt: 0.88 min $[M+H]^+$: 294.1 (met. a)

W1.035

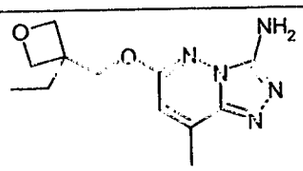
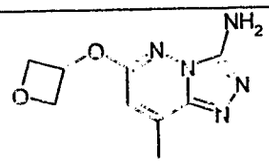
8-Methyl-6-(3-methyloxetan-3-ylmethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



(3-Methyloxetan-3-yl)methanol (1.74 g) was initially charged in DMF (30 ml), admixed under argon with sodium hydride (408 mg) and stirred at 45°C for 0.5 h. Subsequently, 6-chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.002; 1.5 g) was dissolved in DMF (30 ml) and one equivalent of the alkoxide solution (10 ml) was added. After stirring at 45°C for 30 min, a further 0.5 equivalent of alkoxide solution was added, followed by 0.5 eq. each after a further 30 and 60 min. Then the mixture was admixed with water, and the reaction mixture was dried and purified using silica gel (80 g cartridge, dichloromethane/methanol gradient of 0-20% in 60 min). 758 mg of the title compound were obtained.

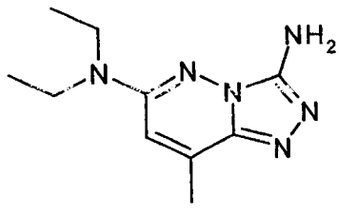
LC-MS rt: 0.49 min $[M+H]^+$: 250.1 (met. b)

The following were prepared analogously:

Number		LC-MS rt	$[M+H]^+$:	Comment:
W1.036		0.57 min	264.1 (met. b)	W2.002 (1 g); product: 550 mg
W1.037		0.62 min	222.1 (met.a)	W2.002 (1 g); product: 605 mg

W1.040

N*6*,N*6*-Diethyl-8-methyl-[1,2,4]triazolo[4,3-b]pyridazine-3,6-diamine

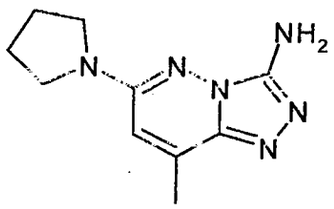
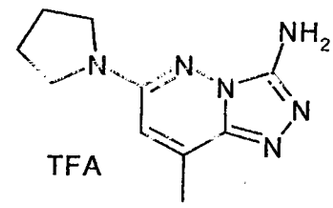


6-Chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.002; 250 mg) was dissolved in abs. DMF (2 ml) and admixed with diethylamine (7 ml). Thereafter, the reaction mixture was placed into a heating block at 80°C with stirring for 11 days. The solvent was then drawn off and the residue was admixed with a little water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. The residue was purified by means of preparative HPLC (met. A), and the clean product fractions were combined, freed of the acetonitrile under reduced pressure, alkalized with saturated potassium carbonate solution and extracted repeatedly with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. 100 mg of the title compound were obtained.

LC-MS rt: 0.70 min $[M+H]^+$: 221.2 (met. b)

W1.041 and W1.041a

8-Methyl-6-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine and 8-methyl-6-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine trifluoroacetate

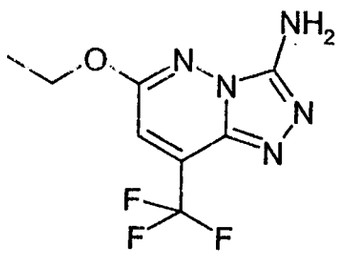
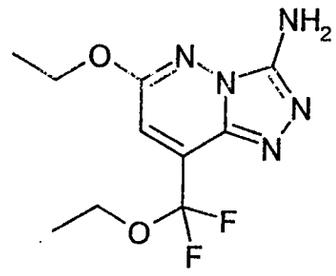
6-Chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.002; 250 mg) was dissolved in DMF (2 ml) and admixed with pyrrolidine (2 ml). Thereafter, the reaction mixture was placed into the heating block at 80°C with stirring for 1.5 h. Subsequently, the solvent was drawn off and the residue was admixed with a little water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. When the residue was dissolved in acetonitrile/water + 0.05 % TFA, a solid precipitated out, which was filtered off with suction and dried. 40 mg of 8-methyl-6-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine were obtained. The mother liquor was purified by means of preparative HPLC (met. A), and the clean product fractions were combined, freed of the acetonitrile under reduced pressure and freeze-dried. 11 mg of 8-methyl-6-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine were obtained as the trifluoroacetic acid salt.

8-Methyl-6-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

LC-MS rt: 0.76 min $[M+H]^+$: 219.1 (met. b)

W1.045 and W1.046

6-Ethoxy-8-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine and 6-ethoxy-8-(ethoxydifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

6-Chloro-8-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.004; 65 mg) was initially charged in ethanol (6 ml) and admixed with sodium ethoxide (21 mg). The reaction mixture was stirred at 50°C for 4 h. After cooling, the mixture was admixed with water and

concentrated. The residue was taken up in ethyl acetate and washed with water three times. The ethyl acetate phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by means of preparative HPLC (met. E). The product-containing fractions, each of them clean, were combined, freed of the acetonitrile, adjusted to pH 9 with sodium hydrogencarbonate and extracted three times with ethyl acetate. The combined organic extracts were dried over sodium carbonate, filtered and concentrated. 15 mg of 6-ethoxy-8-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine and 23 mg of 6-ethoxy-8-(ethoxydifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine were obtained.

6-Ethoxy-8-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine, W1.045

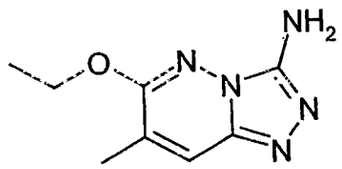
LC-MS rt: 0.70 min $[M+H]^+$: 248.1 (met. b)

6-Ethoxy-8-(ethoxydifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine, W1.046

LC-MS rt: 0.82 min $[M+H]^+$: 272.2 (met. b)

W1.050

6-Ethoxy-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

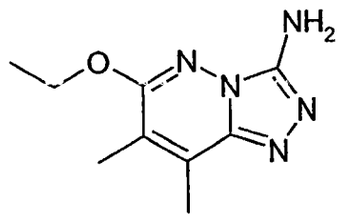


6-Chloro-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.005; 1 g) was dissolved in ethanol (50 ml), admixed under argon with sodium ethoxide (2.2 g) and stirred at 60°C for 1 h. Then the mixture was dried and the residue was purified using a 40 g silica gel cartridge (0-20 % dichloromethane-ethanol gradient in 40 min). The clean product fractions were combined and dried. 480 mg of the title compound were obtained.

LC-MS rt: 2.07 min $[M+H]^+$: 194.1 (met. d)

W1.055

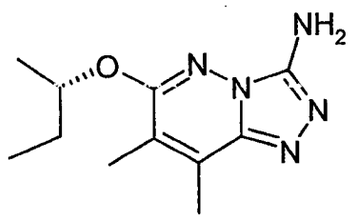
6-Ethoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.006; 4 g) were dissolved in ethanol (120 ml), admixed under argon with sodium ethoxide (5.86 g) and stirred at 60°C for 1h. Then the mixture was dried and the residue was purified using a 40 g silica gel cartridge (0-20 % dichloromethane-ethanol gradient in 40 min). The clean product fractions were combined and dried. 3.24 g of the title compound were obtained, which still contained residual amounts of dichloromethane. LC-MS rt: 0.53 min $[M+H]^+$: 208.1 (met. b)

W1.056

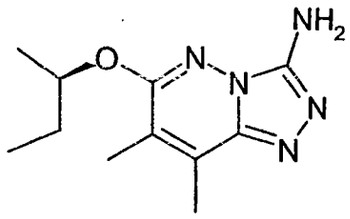
6-((S)-sec-Butoxy)-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



(S)-Butan-2-ol (1.7 ml) was initially charged at RT with stirring and cooled almost to 0°C with an ice bath. Subsequently, the mixture was admixed with portions of sodium hydride (85 mg). The suspension formed was heated to 55°C for 1.5 h and then admixed with portions of 6-chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.006a, 100 mg), suspended in (S)-butan-2-ol (2 ml) and DMF (2 ml). After stirring at 55°C for 1 h, the mixture was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 105 mg of the title compound were isolated in sufficient purity. LC-MS rt: 0.81 min $[M+H]^+$: 236.2 (met. b)

W1.057

6-((R)-sec-Butoxy)-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

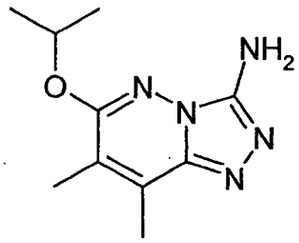


(R)-Butan-2-ol (0.5 ml) was deprotonated analogously to W1.056 with sodium hydride (85 mg) and reacted with 6-chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.006a, 100 mg), suspended in DMF (2 ml), and worked up. 75 mg of the title compound were isolated in sufficient purity.

LC-MS rt: 0.81 min $[M+H]^+$: 236.2 (met. b)

W1.058

6-Isopropoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

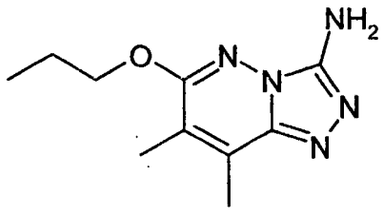


Isopropanol (27 ml) was deprotonated analogously to W1.056 with sodium hydride (1.3 g) and reacted with 6-chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.006a, 1 g), dissolved in isopropanol (10 ml) and DMF (10 ml), and worked up. 847 mg of the title compound were isolated in sufficient purity.

LC-MS rt: 0.74 min $[M+H]^+$: 222.2 (met. b)

W1.059

7,8-Dimethyl-6-propoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



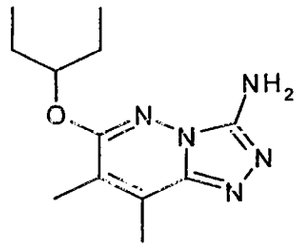
1-Propanol (28 ml) was deprotonated analogously to W1.056 with sodium hydride (1.3 g)

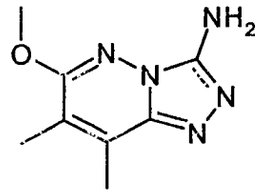
and reacted with 6-chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.006a, 1 g), dissolved in 1-propanol (10 ml) and DMF (10 ml), and worked up. 647 mg of the title compound were isolated in sufficient purity.

LC-MS rt: 0.75 min $[M+H]^+$: 222.2 (met. b)

W1.060 and W1.061

6-(1-Ethylpropoxy)-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine and 6-methoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine





3-Pentanol (1.5 ml) was initially charged at RT with stirring and cooled almost to 0°C with an ice bath. Subsequently, the mixture was admixed with portions of sodium hydride (117 mg). The suspension formed was heated to 55°C for 1.5 h and then admixed with portions of 6-chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.006a, 100 mg), suspended in 3-pentanol (1 ml) and DMF (1.5 ml). After stirring at 55°C for 2 h, the mixture was left to stand at RT overnight, admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. The residue was purified by means of preparative HPLC (met. A), and the clean product fractions were combined, freed of the acetonitrile under reduced pressure, alkalized with saturated potassium carbonate solution and extracted repeatedly with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. 79 mg of 6-(1-ethylpropoxy)-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine and 10 mg of 6-methoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine were obtained, which formed in the reaction mixture as a result of contamination with methanol.

6-(1-Ethylpropoxy)-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine, W1.060

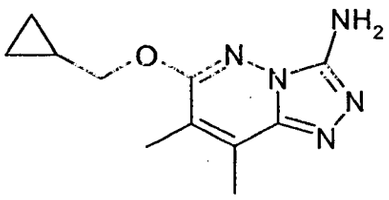
LC-MS rt: 1.30 min $[M+H]^+$: 250.2 (met. a)

6-Methoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine, W1.061

LC-MS rt: 0.88 min $[M+H]^+$: 194.1 (met. a)

W1.062

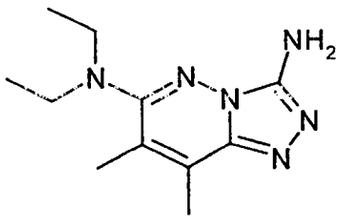
6-Cyclopropylmethoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



Cyclopropylmethanol (2.84 ml) was initially charged in DMF (20 ml), admixed under argon with sodium hydride (862 mg) and stirred at 50°C for 1 h. Subsequently, 6-chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.006, 2 g), dissolved in DMF (20 ml), and one equivalent of the alkoxide solution were added. After stirring at 50°C for one hour, two further equivalents of alkoxide solution were added and the mixture was stirred further at 50°C. Then the reaction mixture was dried and purified using silica gel (40 g cartridge, dichloromethane/methanol gradient of 0-10% in 40 min). 625 mg of the title compound were obtained. LC-MS rt: 0.62 min $[M+H]^+$: 234.1 (met. b)

W1.065

N*6*,N*6*-Diethyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-3,6-diamine



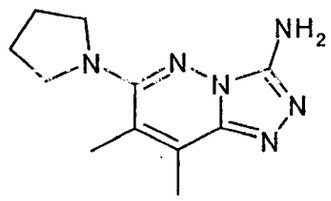
6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.006a, 800 mg and 650 mg divided between 2 microwave vessels) was initially charged each dissolved in 12 ml of diethylamine and admixed with 1-butyl-3-methylimidazolium hexafluorophosphate (150 µl). Subsequently, they were placed into the microwave at 180°C for 4 h. In order to complete the reaction, they were placed again into the microwave at 180°C for 4 h and then

left to stand overnight. The two reaction mixtures were combined in a round-bottom flask and dried. The residue was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. The residue was purified by means of preparative HPLC (met. F), and the clean product fractions were combined, freed of the acetonitrile under reduced pressure, alkalized with saturated potassium carbonate solution and extracted repeatedly with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. 900 mg of the title compound were obtained.

LC-MS rt: 0.77 min $[M+H]^+$: 235.2 (met. b)

W1.066

7,8-Dimethyl-6-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

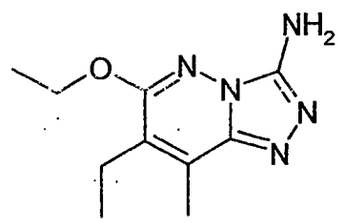


6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.006a, 500 mg) were initially charged in pyrrolidine (5 ml) at RT while stirring. Then the mixture was heated to 65°C for 4 h. Thereafter, the pyrrolidine was drawn off, and the residue was taken up with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. 438 mg of the title compound were obtained.

LC-MS rt: 0.72 min $[M+H]^+$: 233.2 (met. b)

W1.070

6-Ethoxy-7-ethyl-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

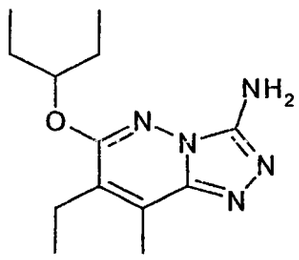


6-Chloro-7-ethyl-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.007; 380 mg) was initially charged in ethanol (45 ml) at RT while stirring, admixed with sodium ethoxide (244 mg) and heated to 55°C for 3 h. Then a further equivalent of sodium ethoxide was added and the mixture was stirred once again at 55°C for 3 h. After leaving to stand over the weekend, the mixture was dried, and the residue was taken up with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. 387 mg of the title compound were obtained.

LC-MS rt: 0.76 min $[M+H]^+$: 222.2 (met. b)

W1.071

7-Ethyl-6-(1-ethylpropoxy)-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

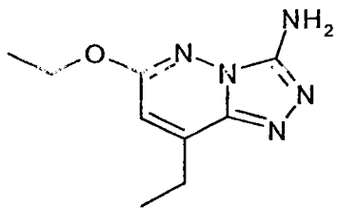


3-Pentanol (2.5 ml) was initially charged at RT with stirring. Thereafter, sodium hydride (91 mg) was added while cooling with ice. After stirring at 55°C for 2.5 h, 6-chloro-7-ethyl-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.007; 120 mg), dissolved in 3-pentanol (2 ml) and DMF (4 ml), was added dropwise. After stirring for 1 h, the mixture was left to stand at RT overnight, and the reaction mixture was admixed with water and dichloromethane and then extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 126 mg of the title compound were obtained.

LC-MS rt: 0.90 min $[M+H]^+$: 264.2 (met. b)

W1.075

6-Ethoxy-8-ethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

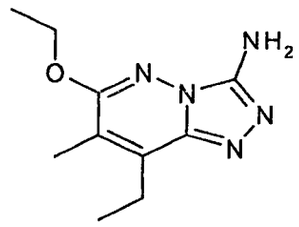


6-Chloro-8-ethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.003; 700 mg) was dissolved in ethanol (100 ml) while stirring. Thereafter, the reaction mixture was admixed with sodium ethoxide (724 mg) and stirred at RT for 2 h. Subsequently, the mixture was heated to 45°C for 3 h. After the solvent had been drawn off, the residue was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 670 mg of the title compound were obtained.

LC-MS rt: 0.64 min $[M+H]^+$: 208.2 (met. b)

W1.076

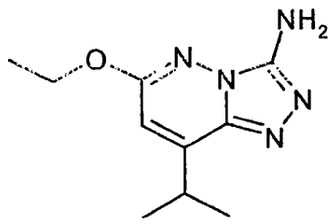
6-Ethoxy-8-ethyl-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

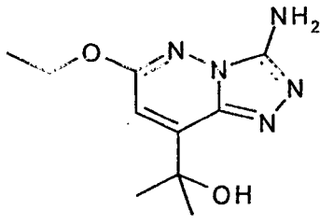


6-Chloro-8-ethyl-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.008, 273 mg) was dissolved in abs. ethanol (20 ml) while stirring. Thereafter, the reaction mixture was admixed with sodium ethoxide (176 mg) and stirred at RT for 3.5 h. After standing over the weekend, the solvent was drawn off, and the residue was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 230 mg of the title compound were obtained. LC-MS rt: 0.75 min $[M+H]^+$: 222.2 (met. b)

W1.080 and W1.081

6-Ethoxy-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine and 2-(3-amino-6-ethoxy-[1,2,4]triazolo[4,3-b]pyridazin-8-yl)propan-2-ol





6-Chloro-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.009, 77 mg) was initially charged in ethanol (8 ml) while stirring at RT and admixed with sodium ethoxide (50 mg). After stirring for 4.5 h, the mixture was left to stand overnight and then the solvent was drawn off. The residue was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 52 mg of the title compounds were obtained as a mixture (according to ^{1}H NMR, ~70:30 in favor of 6-ethoxy-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine).

6-Ethoxy-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine, W1.080

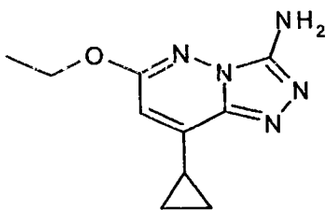
LC-MS rt: 0.76 min $[M+H]^+$: 222.2 (met. b)

2-(3-Amino-6-ethoxy-[1,2,4]triazolo[4,3-b]pyridazin-8-yl)propan-2-ol, W1.081

LC-MS rt: 0.40 min $[M+H]^+$: 238.1 (met. b)

W1.082

8-Cyclopropyl-6-ethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

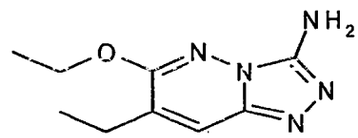


6-Chloro-8-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.010, 77 mg) was initially charged in ethanol (10 ml) while stirring at RT and admixed with sodium ethoxide (67 mg). After stirring for 4.5 h, the mixture was left to stand overnight and then the solvent was drawn off. The residue was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 91 mg of the title compound were obtained.

LC-MS rt: 0.71 min $[M+H]^+$: 220.2 (met. b)

W1.085

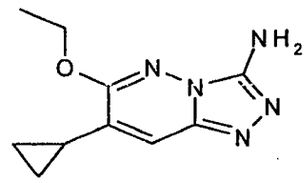
6-Ethoxy-7-ethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7-ethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine trifluoroacetate salt (W2.011, 82 mg) was reacted and worked up analogously to W1.075. 77 mg of the title compound were obtained. LC-MS rt: 0.69 min $[M+H]^+$: 208.2 (met. b)

W1.086

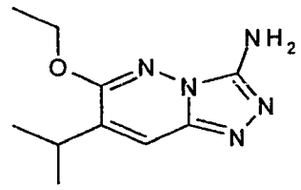
7-Cyclopropyl-6-ethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.012, 30 mg) was reacted and worked up analogously to W1.075. 31 mg of the title compound were obtained. LC-MS rt: 0.70 min $[M+H]^+$: 220.2 (met. b)

W1.087

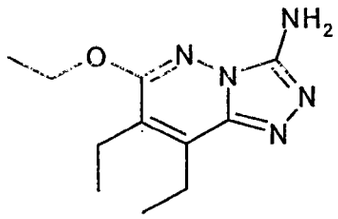
6-Ethoxy-7-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.013, 30 mg) was reacted and worked up analogously to W1.075. 31 mg of the title compound were obtained.
LC-MS rt: 0.76 min $[M+H]^+$: 222.2 (met. b)

W1.090

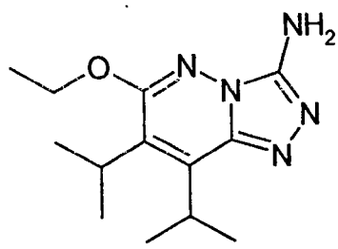
6-Ethoxy-7,8-diethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7,8-diethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.014, 0.1 g) was dissolved in ethanol (13 ml) while stirring and under argon. Thereafter, the reaction mixture was admixed with sodium ethoxide (61 mg) and stirred at RT for 1 h, then at 55°C for 30 min. Subsequently, a further 2 equivalents of sodium ethoxide were added and the mixture was stirred at 55°C for 4.5 h. After another 1 equivalent of sodium ethoxide had been added, the mixture was stirred at 55°C for 2.5 h and left to stand over the weekend. The solvent was then drawn off, and the residue was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 92 mg of the title compound were obtained. LC-MS rt: 0.80 min $[M+H]^+$: 236.2 (met. b)

W1.091

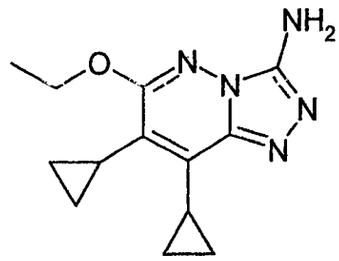
6-Ethoxy-7,8-diisopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7,8-diisopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.015, 0.1 g) was dissolved in ethanol (15 ml) while stirring and under argon. Thereafter, the reaction mixture was admixed with sodium ethoxide (110 mg) and stirred at RT for 1 h, then at 55°C for 1 h. Subsequently, the mixture was left to stand overnight, then stirred again at 55°C for 7.5 h and then the solvent was drawn off, and the residue was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 100 mg of the title compound were obtained. LC-MS rt: 0.90 min $[M+H]^+$: 264.2 (met. b)

W1.092

7,8-Dicyclopropyl-6-ethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

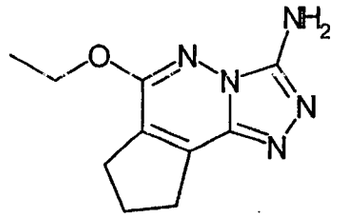


6-Chloro-7,8-dicyclopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.016, 0.1 g) was dissolved in ethanol (20 ml) while stirring and under argon. Thereafter, the reaction mixture was admixed with sodium ethoxide (110 mg) and stirred at RT for 1 h, then at 55°C for 1 h. Subsequently, the mixture was left to stand overnight and then heated to reflux for 7.5 h. After standing over the weekend, the solvent was drawn off, and the residue was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 100 mg of the title compound were obtained.

LC-MS rt: 0.84 min $[M+H]^+$: 260.2 (met. b)

W1.095

6-Ethoxy-8,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

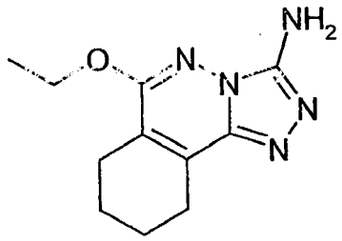


6-Chloro-8,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.017, 1.0 g) was dissolved in ethanol (50 ml) while stirring and under argon. Thereafter, the reaction mixture was admixed with sodium ethoxide (1.41 g) and stirred at 60°C for 1 h. After the solvent had been drawn off, the residue was purified using a 40 g silica gel cartridge (0-20 % dichloromethane-ethanol gradient in 60 min). The clean product fractions were combined and dried. 662 mg of the title compound were obtained.

LC-MS rt: 0.56 $[M+H]^+$: 220.1 (met. b)

W1.096

6-Ethoxy-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazin-3-ylamine

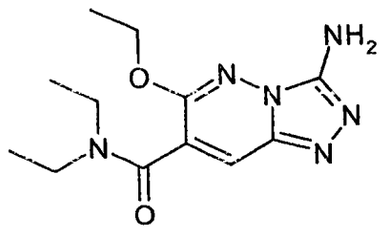


6-Chloro-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazin-3-ylamine (W2.018, 1.0 g) was dissolved in ethanol (50 ml) while stirring and under argon. Thereafter, the reaction mixture was admixed with sodium ethoxide (1.34 g) and stirred at 60°C for 1 h. After the solvent had been drawn off, the residue was purified using a 40 g silica gel cartridge (0-20 % dichloromethane-ethanol gradient in 40 min). The clean product fractions were combined and dried. 491 mg of the title compound were obtained.

LC-MS rt: 0.95 $[M+H]^+$: 234.1 (met. a)

W1.100

N,N-Diethyl-3-amino-6-ethoxy-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide

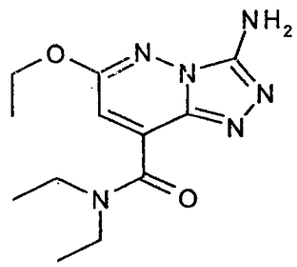


N,N-Diethyl-3-amino-6-chloro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide (W2.019, 50 mg) was initially charged in ethanol (5 ml) and admixed with sodium ethoxide (28 mg) while stirring. After stirring at RT for 7 h and leaving to stand overnight, the solvent was drawn off and the mixture was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 51 mg of the title compound were obtained.

LC-MS rt: 1.00 min $[M+H]^+$: 279.2 (met. b)

W1.101

N,N-Diethyl-3-amino-6-ethoxy-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxamide

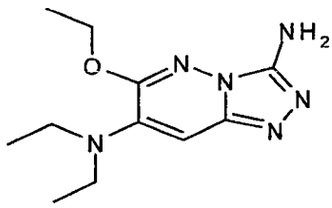


N,N-Diethyl-3-amino-6-chloro-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxamide (W2.020, 50 mg) was prepared analogously to W1.100. 51 mg of the title compound were obtained.

LC-MS rt: 1.04 min $[M+H]^+$: 279.2 (met. b)

W1.102

6-Ethoxy-N*7*,N*7*-diethyl-[1,2,4]triazolo[4,3-b]pyridazine-3,7-diamine

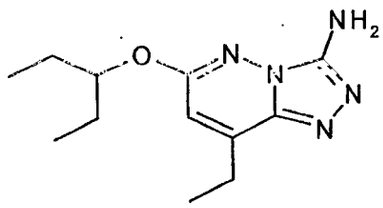


6-Chloro-N*7*,N*7*-diethyl-[1,2,4]triazolo[4,3-b]pyridazine-3,7-diamine (W2.021, 38 mg) were initially charged in ethanol (7 ml) and admixed with sodium ethoxide (24 mg). The reaction mixture stirred at RT for 4 h. It was then stirred at 45°C for another 2 h. Subsequently, the mixture was dried, the residue was admixed with water and extracted three times with EA, and the combined EA phases were dried with magnesium sulfate, filtered and concentrated. 30 mg of the title compound were obtained as a crude product, which was clean enough for the next reaction.

LC-MS rt: 1.13 min $[M+H]^+$: 251.2 (met. a)

W1.105

8-Ethyl-6-(1-ethylpropoxy)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

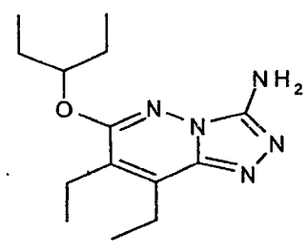


3-Pentanol (1.2 ml) was initially charged at RT with stirring. Thereafter, sodium hydride (77 mg) was added while cooling with ice. After stirring at 55°C for 2.5 h, 6-chloro-8-ethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.003, 60 mg), dissolved in 3-pentanol (1.5 ml) and 4 ml of DMF (4 ml), was added dropwise. After stirring for 2 h, the reaction mixture was left to stand at RT overnight, admixed with water and dichloromethane and then extracted three times more with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 70 mg of the title compound were obtained,

LC-MS rt: 0.87 min $[M+H]^+$: 250.2 (met. b)

W1.106

7,8-Diethyl-6-(1-ethylpropoxy)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

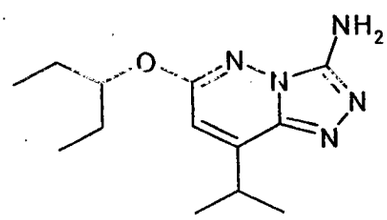


6-Chloro-7,8-diethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.014, 100 mg) was reacted and worked up analogously to W1.071. 110 mg of the title compound were obtained.

LC-MS rt: 0.93 min $[M+H]^+$: 278.2 (met. b)

W1.107

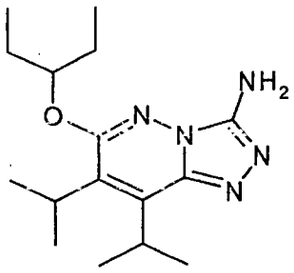
6-(1-Ethylpropoxy)-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.009, 80 mg) was reacted and worked up analogously to W1.071. The crude product was then purified by means of preparative HPLC (met. A), and the clean product fractions were combined, freed of the acetonitrile under reduced pressure, alkalized with saturated potassium carbonate solution and extracted repeatedly with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. 51 mg of the title compound were obtained. LC-MS rt: 0.91 min $[M+H]^+$: 264.2 (met. b)

W1.108

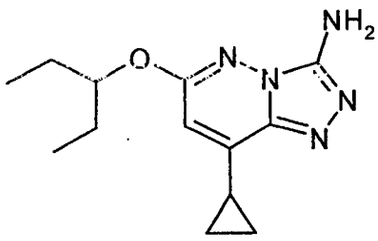
6-(1-Ethylpropoxy)-7,8-diisopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7,8-diisopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.015, 100 mg) was reacted, worked up and purified analogously to W1.107. 72 mg of the title compound were obtained. LC-MS rt: 1.01 min $[M+H]^+$: 306.3 (met. b)

W1.109

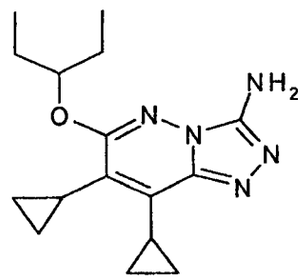
8-Cyclopropyl-6-(1-ethylpropoxy)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-8-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.010, 100 mg) was reacted, worked up and purified analogously to W1.107. 74 mg of the title compound were obtained. LC-MS rt: 0.89 min $[M+H]^+$: 262.2 (met. b)

W1.110

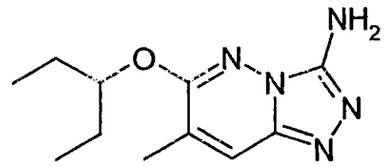
7,8-Dicyclopropyl-6-(1-ethylpropoxy)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7,8-dicyclopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.016, 100 mg) was reacted, worked up and purified analogously to W1.107. 35 mg of the title compound were obtained. LC-MS rt: 0.95 min $[M+H]^+$: 302.2 (met. b)

W1.111

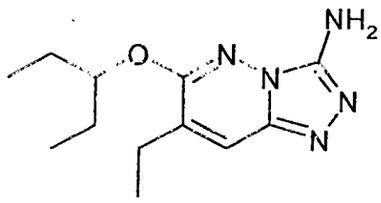
6-(1-Ethylpropoxy)-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



3-Pentanol (30 ml) was initially charged under argon, admixed with sodium hydride (1.48 g) and stirred at 50°C for 1 h. Subsequently, 6-chloro-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.005, 1.88 g), dissolved in 3-pentanol (130 ml) and DMF (60 ml), was slowly added dropwise within 1 h. After stirring for 1 h, the mixture was concentrated, and the residue was admixed with water and extracted four times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified using an 80 g silica gel cartridge (0-10 % dichloromethane-methanol gradient in 40 min). The clean product fractions were combined and dried. 1.25 g of the title compound were obtained. LC-MS rt: 2.60 min $[M+H]^+$: 236.1 (met. e)

W1.112

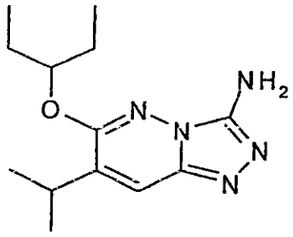
7-Ethyl-6-(1-ethylpropoxy)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7-ethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.011, 150 mg) was reacted, worked up and purified analogously to W1.107. 103 mg of the title compound were obtained.
LC-MS rt: 0.87 min $[M+H]^+$: 250.2 (met. b)

W1.113

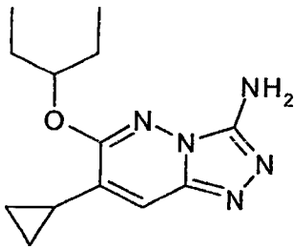
6-(1-Ethylpropoxy)-7-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.013, 100 mg) was reacted and worked up analogously to W1.071. 132 mg of the title compound were obtained, which was still contaminated with a little DMF.
LC-MS rt: 0.90 min $[M+H]^+$: 264.2 (met. b)

W1.114

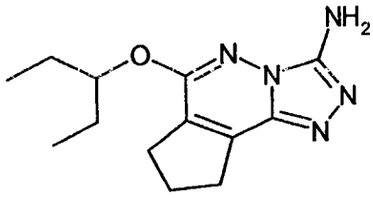
7-Cyclopropyl-6-(1-ethylpropoxy)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-7-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.012, 100 mg) was reacted and worked up analogously to W1.071. 116 mg of the title compound were obtained.
LC-MS rt: 0.87 min $[M+H]^+$: 262.2 (met. b)

W1.115

6-(1-Ethylpropoxy)-8,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

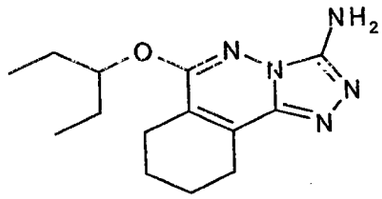


3-Pentanol (20 ml) was initially charged under argon, admixed with sodium hydride (991 mg) and stirred at 50°C for 1 h. Subsequently, 6-chloro-8,9-dihydro-7H-cyclopenta[d][1,2,4]-triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.017, 2.0 g), dissolved in 3-pentanol (20 ml) and DMF (100 ml), was slowly added dropwise within 1 h. After stirring for 1 h, the mixture was concentrated, and the residue was admixed with water and extracted four times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified using a 40 g silica gel cartridge (dichloromethane-methanol gradient 0-10 % in 50 min). The clean product fractions were combined and dried. 1.04 g of the title compound were obtained.

LC-MS rt: 2.82 min $[M+H]^+$: 262.1 (met. e)

W1.116

6-(1-Ethylpropoxy)-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazin-3-ylamine



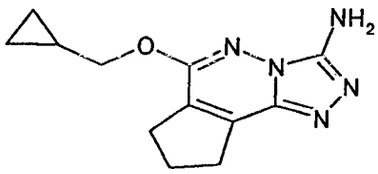
3-Pentanol (20 ml) was initially charged under argon, admixed with sodium hydride (946 mg) and stirred at 50°C for 1 h. Subsequently, 6-chloro-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]-phthalazin-3-ylamine hydrobromide (W2.018, 1.88 g), dissolved in 3-pentanol (20 ml) and DMF (100 ml), was slowly added dropwise within 1 h. After stirring for 1 h, the mixture was concentrated, and the residue was admixed with water and extracted four times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified using a 40 g silica gel cartridge (0-10 % dichloromethane-methanol gradient in 50 min). The clean product fractions were combined

and dried. 0.8 g of the title compound was obtained.

LC-MS rt: 1.15 min $[M+H]^+$: 276.1 (met. a)

W1.120

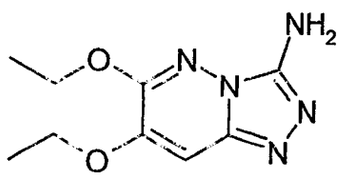
6-Cyclopropylmethoxy-8,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



Cyclopropylmethanol (1.78 ml) was initially charged in DMF (25 ml). Subsequently, the mixture was admixed with sodium hydride (541 mg) under argon and stirred at 45°C for 0.5 h. Subsequently, 6-chloro-8,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.017, 1.31 g) was dissolved in DMF (20 ml) and 11.25 ml of the alkoxide solution were added in portions at 45°C over 90 min. Then the mixture was stirred at 45°C for another hour. After adding a little water, the mixture was dried and purified using silica gel (80 g cartridge, dichloromethane/methanol gradient of 0-20% in 60 min). 528 mg of the title compound were obtained. LC-MS rt: 0.63 min $[M+H]^+$: 246.1 (met. b)

W1.125

6,7-Diethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



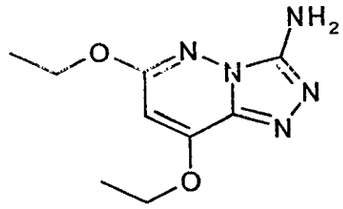
(5,6-Diethoxy-pyridazin-3-yl)hydrazine (W3.120; 50 mg) was initially charged in a mixture of ethanol (3.5 ml) and water (0.75 ml) at RT while stirring. Thereafter, cyanogen bromide (55 mg, dissolved in 0.75 ml of ethanol and 0.15 ml of water) was cautiously added dropwise. After stirring for 7 h, the mixture was left to stand overnight. Thereafter, a further 2 equivalents of cyanogen bromide, dissolved in 0.75 ml of ethanol and 0.15 ml of water, were added and the mixture was stirred further at RT for 2 h and then at 55°C for 8 h. After cooling, the solvent was drawn off and the residue was admixed with water. After it had been

alkalized with saturated potassium carbonate solution, it was extracted four times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. The residue was purified by means of preparative HPLC (met. A). The clean product fractions were combined, freed of the acetonitrile under reduced pressure, alkalized with saturated potassium carbonate solution and extracted four times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 36 mg of the title compound were obtained.

LC-MS rt: 0.54 min $[M+H]^+$: 224.2 (met. b)

W1.126

6,8-Diethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

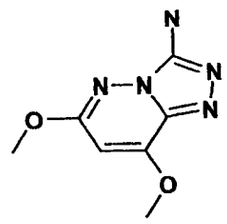


6-Chloro-8-methanesulfonyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.126; 60 mg, 0.24 mmol) was dissolved in ethanol (5 ml), sodium ethoxide (500 µl, 21 % in ethanol) was added and the mixture was heated to 50°C for 5 h. The mixture was concentrated and the residue was purified by flash chromatography (dichloromethane:methanol). Yield: 54 mg

LC-MS rt: 0.52 min $[M+H]^+$: 224.1 (met. b)

W1.127

6,8-Dimethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



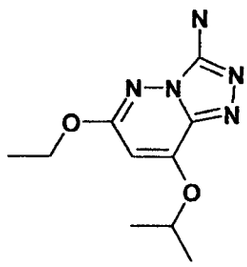
6-Chloro-8-methanesulfonyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.126; 100 mg, 0.40 mmol) was dissolved in methanol (10 ml), and sodium methoxide solution (0.75 ml, 4.04 mmol) was added. The mixture was heated to reflux for 3 h, then concentrated, and the

residue was dissolved in water and a pH of 6 was established by adding aqueous hydrochloric acid. The mixture was extracted with EA and the combined organic phases were dried and concentrated. The remaining residue was purified by flash chromatography (dichloromethane:MeOH). Yield: 30 mg

LC-MS rt: 0.14 min $[M+H]^+$: 196.1 (met. b)

W1.128

6-Ethoxy-8-isopropoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

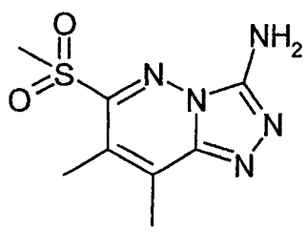


6,8-Diethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W1.126; 80 mg, 0.358 mmol) was dissolved in isopropanol (10 ml), and sodium isopropoxide (297 mg) was added. The mixture was heated to 85°C for 1 h and concentrated, the residue was dissolved in water and a pH of 6 was established by adding aqueous hydrochloric acid. The mixture was extracted with ethyl acetate and the combined organic phases were dried and concentrated. The remaining residue was purified by flash chromatography (dichloromethane:MeOH). Yield: 58 mg.

LC-MS rt: 0.58 min $[M+H]^+$: 238.2 (met. b)

W1.130

6-Methanesulfonyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

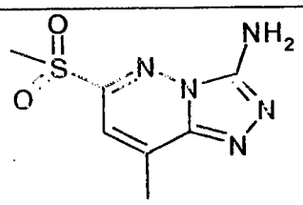


6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.006; 1.0 g) and sodium sulfinate (916 mg) were dissolved in DMF (6 ml) and stirred in a microwave at 150°C for 45 min. After the solvent had been drawn off, the residue was

purified using silica gel (40 g cartridge, dichloromethane/methanol gradient of 0-20% in 60 min). 1.02 g of the title compound were obtained.

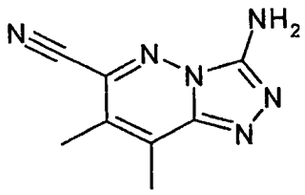
LC-MS rt: 0.33 min $[M+H]^+$: 242.1 (met. b)

The following was prepared analogously:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.131		0.20 min	175.1(met. b)	W2.002; 5.1 g; sulfinate (4.9 g); 7 h at 100°C; product: 6.3 g

W1.135

3-Amino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carbonitrile

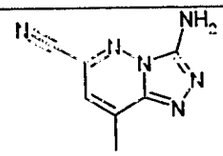


6-Methanesulfonyl-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W1.130; 1.0 g) was dissolved in DMF (30 ml) and admixed with potassium cyanide (405 mg). After stirring at 100°C for 1 h, the mixture was dried. The residue was stirred in EA and chromatographed using a short silica gel column with EA. Fractions concentrated by rotary evaporation.

560 mg of the title compound were obtained.

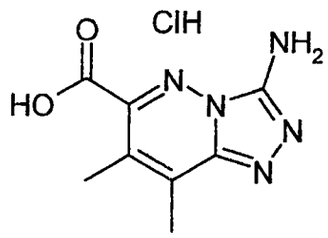
LC-MS rt: 0.27 min $[M+H]^+$: 189.1 (met. b)

The following was prepared analogously:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.136		0.20 min	175.1 (met. b)	W1.131: 6.3 g; KCN (2.7 g); 7 h at 100°C; product: 870 mg

W1.140

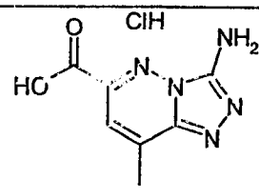
3-Amino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid hydrochloride



3-Amino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carbonitrile (W1.135; 600 mg) was admixed with concentrated hydrochloric acid (20 ml) and kept at reflux for 5 h. Subsequently, the hydrochloric acid was drawn off, and the residue was taken up with water and freeze-dried. 790 mg of the title compound were obtained, which was of sufficient purity for the next reaction.

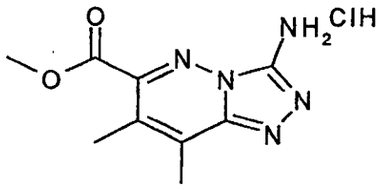
LC-MS rt: 0.19 min $[M+H]^+$: 189.1 (met. c)

The following was prepared analogously:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.41		0.11 min	194.1 (met. b)	W1.136: 860 mg; HCl (30 ml); 2 h RF; product: 1.7 g

W1.145

Methyl 3-amino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylate hydrochloride

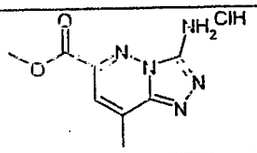


3-Amino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid hydrochloride (W1.140; 780 mg) was dissolved in methanol (40 ml) and thionyl chloride (1.9 ml) was slowly added dropwise, and then the mixture was stirred at 65°C. After 2.5 h, the mixture was dried and the residue was purified using silica gel (24 g cartridge, dichloromethane/methanol

gradient of 0-20% in 60 min). 602 mg of the title compound were obtained.

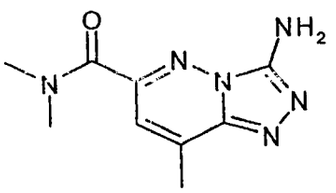
LC-MS rt: 0.37 min $[M+H]^+$: 222.1 (met. b)

The following was prepared analogously:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.146		0.20 min	208.1 (met. b)	W1.141: 600 mg; thionyl chloride (1.53 ml); 1.5 h 65°C; product: 429 mg

W1.150

N-Methyl-3-amino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide

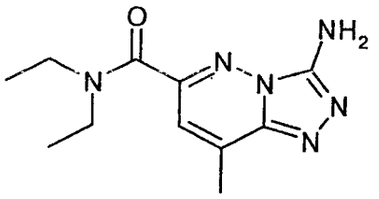


Methyl 3-amino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylate (W1.146; 210 mg) was dissolved in methanol (4 ml), cooled to 0°C, slowly admixed dropwise with dimethylamine (2.02 ml; 2 M in THF) and stirred at 0°C. After 3 h, a further 5 equivalents of dimethylamine solution were added and the mixture was stirred at 40°C for 4 h. After standing overnight, another 5 equivalents of dimethylamine solution were added and the mixture was stirred at 40°C for a further 8 h. After standing overnight again, a further 5 equivalents of dimethylamine solution were added and then the mixture was stirred at 100°C in a microwave for 30 min. Subsequently, the mixture was concentrated and purified using silica gel (24 g cartridge, dichloromethane/methanol gradient of 0-20% in 60 min). 92 mg of the title compound were obtained.

LC-MS rt: 0.13 min $[M+H]^+$: 221.1 (met. b)

W1.152

N-Ethyl-3-amino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide

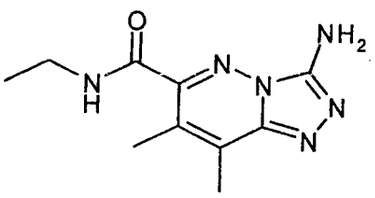


3-Amino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid hydrochloride (W1.141; 300 mg) was dissolved in DMF (6 ml) and admixed with O-[(ethoxycarbonyl)-cyanomethyleneamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU; 429 mg) and diethylamine (573 mg). After 2 h, the DMF was drawn off and the residue was purified using silica gel (24 g cartridge, dichloromethane/ methanol gradient of 0-20% in 60 min). The product was taken up with water and freeze-dried. In order to remove residual diethylamine, the mixture was chromatographed using a short column (dichloromethane/ methanol 95:5). 112 mg of the title compound were obtained, which was still contaminated with diethylamine.

LC-MS rt: 0.40 min $[M+H]^+$: 249.1 (met. b)

W1.154

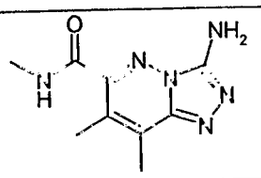
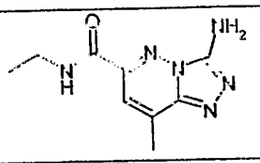
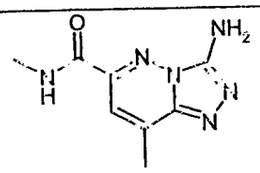
N-Ethyl-3-amino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide



Methyl 3-amino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylate hydrochloride (W1.145; 200 mg) was dissolved in methanol, cooled to 0°C, slowly admixed dropwise with ethylamine (1.81 ml; 2 M in THF) and stirred at 0°C for 6 h. Then a further equivalent of ethylamine was added and the mixture was left to stand at RT over the weekend. Subsequently, the mixture was concentrated and purified using silica gel (24 g cartridge, dichloromethane/methanol gradient of 0-20% in 60 min). 149 mg of the title compound were obtained.

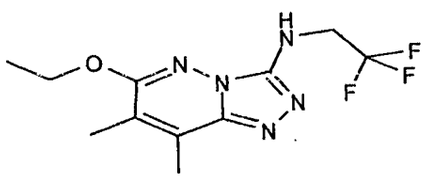
LC-MS rt: 0.21 min $[M+H]^+$: 235.1 (met. b)

The following were prepared analogously:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.155		0.58 min	221.1 (met. c)	W1.145: 200 mg; methylamine (2 M in THF); product: 113 mg
W1.156		0.28 min	221.1 (met. b)	W1.146: 210 mg; ethylamine (4.7 eq.; 2 M in THF); product: 164 mg
W1.157		0.16 min	207.1 (met. b)	W1.146: 225 mg; methylamine (4.7 eq.; 2 M in THF); product: 113 mg

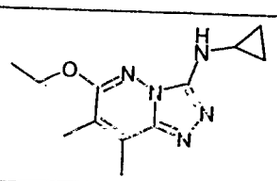
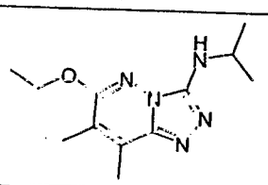
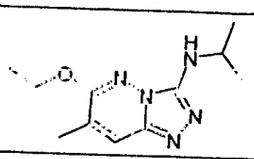
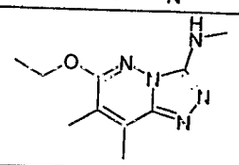
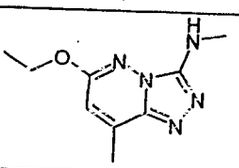
W1.165

(6-Ethoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)(2,2,2-trifluoroethyl)amine



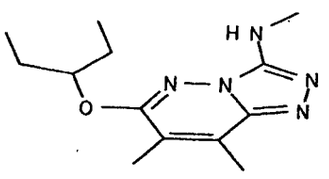
(6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)(2,2,2-trifluoroethyl)amine (W2.150; 330 mg) was initially charged in ethanol (25 ml) and admixed with sodium ethoxide (90 mg). The reaction mixture was stirred at 50°C for 4 h, then further sodium ethoxide (10 mg) was added and the mixture was stirred further at 50°C for 3 h. After standing overnight, the mixture was admixed with water and dried. The residue was taken up in EA and washed three times with water. The EA phase was dried over sodium sulfate, filtered and concentrated. 340 mg of the title compound were obtained. LC-MS rt: 0.82 min $[M+H]^+$: 290.2 (met. b)

The following were prepared analogously:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.166		0.75 min	248.2 (met. b)	W2.166; 690 mg; product: 508 mg
W1.167		0.73 min	236.2 (met. b)	W2.167; 500 mg; product: 380 mg
W1.168		0.78 min	250.2 (met. b)	W2.168; 78 mg; product: 57 mg
W1.169		0.71 min	222.2 (met. b)	W2.169; 50 mg; product: 27 mg
W1.170		0.49 min	208.2 (met. b)	W2.170; 105 mg; product: 70 mg

W1.175

[6-(1-Ethylpropoxy)-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl]methylamine

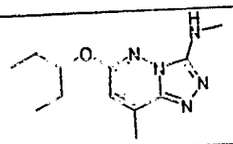


3-Pentanol (1.2 ml) was initially charged at RT with stirring. Thereafter, sodium hydride (77 mg) was added while cooling with ice. After stirring at 55°C for 3 h, (6-chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamine (W2.169; 50 mg), dissolved in 3-pentanol (1 ml) and DMF (2 ml), was added dropwise. After stirring for 2 h, the reaction mixture was left to stand at RT overnight, admixed with water and dichloromethane and then extracted three times more with dichloromethane. The combined organic phases were dried

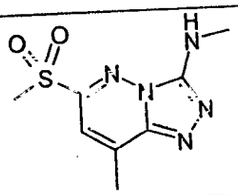
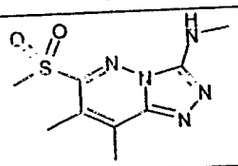
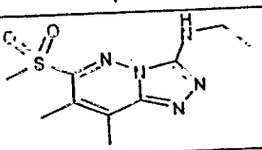
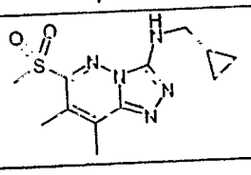
over magnesium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 44 mg of the title compound were obtained.

LC-MS rt: 0.86 min $[M+H]^+$: 264.2 (met. b)

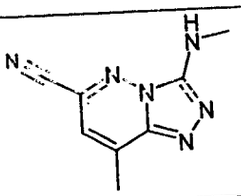
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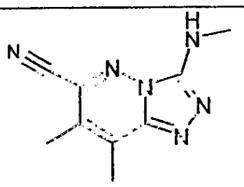
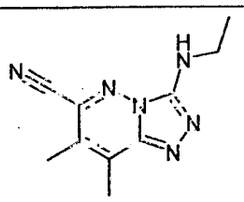
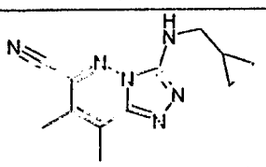
Number		LC-MS rt	$[M+H]^+$	Comment:
W1.176		0.82 min	250.2 (met. b)	W2.170: 105 mg; product: 60 mg

The following were prepared analogously to W1.130:

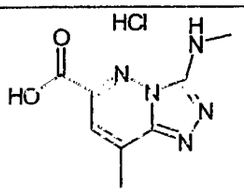
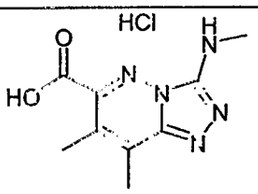
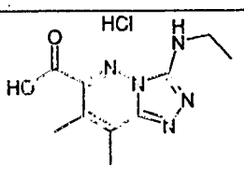
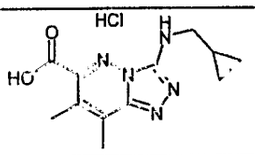
Number		LC-MS rt	$[M+H]^+$	Comment:
W1.189		0.24 min	242.1 (met. b)	W2.170: 7.73 g; product: 6.22 g
W1.190		0.43 min	256.0 (met. b)	W2.169.08 g; product: 4.84 g
W1.191		0.51 min	270.1 (met. b)	W2.191: 7.89 g; product: 5.38 g
W1.192		0.60 min	296.1 (met. b)	W2.192: 9.44 g; product: 5.45 g

The following were prepared analogously to W1.135:

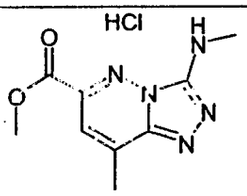
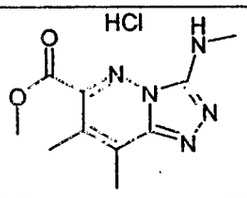
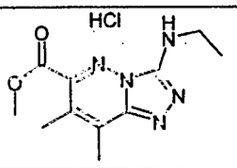
Number		LC-MS rt	$[M+H]^+$	Comment:
W1.199		0.24 min	189.1 (met. b)	W1.189: 5.00 g; product: 1.74 g

W1.200		0.39 min	203.1 (met. b)	W1.190: 4.83 g; product: 3.50 g
W1.201		0.50 min	217.1 (met. b)	W1.191: 5.37 g; product: 3.18 g
W1.202		0.63 min	243.1 (met. b)	W1.192: 5.44 g; product: 3.84 g

The following were prepared analogously to W1.140:

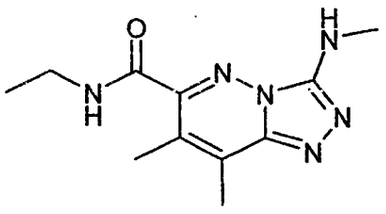
Number		LC-MS rt	$[M+H]^+$	Comment:
W1.209		0.10 min	208.1 (met. b)	W1.199: 1.73 g; product: 2.77 g
W1.210		0.23 min	222.1 (met. c)	W1.200: 3.50 g; product: 5.27 g
W1.211		0.47 min	236.1 (met. c)	W1.201: 3.17 g; product: 4.68 g
W1.212		0.17 min	262.1 (met. b)	W1.202: 3.83 g; product: 5.47 g

The following were prepared analogously to W1.145:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.219		0.29 min	222.1 (met. b)	W1.210: 2.77 g; product: 2.56 g
W1.220		0.41 min	236.1 (met. b)	W1.210: 4.98 g; product: 4.11 g
W1.221		0.50 min	250.1 (met. b)	W1.211: 4.67 g; product: 4.06 g

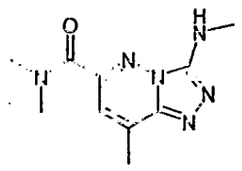
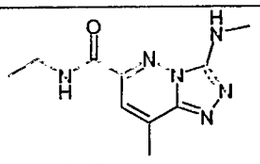
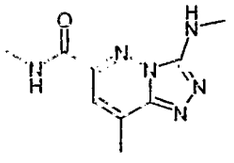
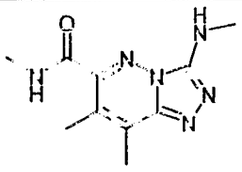
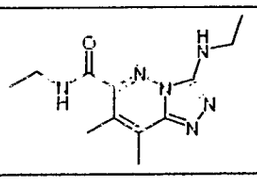
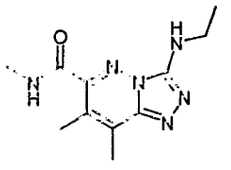
W1.250

N-Ethyl-7,8-dimethyl-3-methylamino-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide

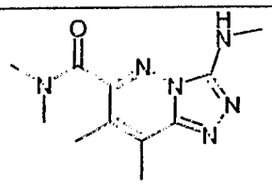


Methyl 7,8-dimethyl-3-methylamino-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylate hydrochloride (W1.220; 1.3 g) was dissolved in methanol (30 ml), cooled to 0°C, slowly admixed dropwise with ethylamine (11.44 ml; 2 M in THF) and stirred at 0°C for 6 h. Then four further equivalents ethylamine were added and the mixture was left to stand at RT over the weekend. Subsequently, the mixture was concentrated and purified using silica gel (40 g cartridge, dichloromethane/methanol gradient of 0-20% in 60 min). 1.12 g of the title compound were obtained. LC-MS rt: 0.81 min $[M+H]^+$: 249.1 (met. b)

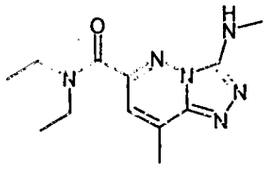
The following were prepared analogously:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.251		0.14 min	235.1 (met. b)	W1.219: 770 mg; dimethylamine (5+2 eq.; 2 M in THF); product: 542 mg
W1.252		0.39 min	235.1 (met. b)	W1.219; 850 mg; ethylamine (4.7 eq.; 2 M in THF); product: 590 mg
W1.253		0.18 min	221.1 (met. b)	W1.219; 850 mg; methylamine (4.7+2 eq.; 2 M in THF); product: 530 mg
W1.254		0.68 min	235.1 (met. b)	W1.220; 800 mg; methylamine (4.7+2 eq.; 2 M in THF); product: 629 mg
W1.255		0.86 min	263.1 (met. b)	W1.221; 800 mg; ethylamine (4.7+4 eq.; 2 M in THF); product: 732 mg
W1.256		0.79 min	249.1 (met. b)	W1.221; 800 mg; methylamine (4.7+2 eq.; 2 M in THF); product: 612 mg

W1.265 was prepared analogously to W1.150:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.265		0.16 min	249.1 (met. b)	W1.220; 800 mg; dimethylamine (5+5+5 eq., 2 M in THF); product: 330 mg

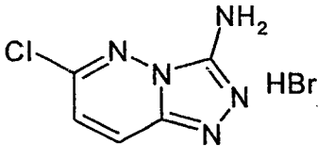
The following was prepared analogously to W1.152:

Number		LC-MS rt	$[M+H]^+$	Comment:
W1.270		0.45 min	263.1 (met. b)	W1.209; 860 mg; diethylamine (1.81 ml); TOTU 1.16 g; product: 251 mg (no freeze-drying and additional column)

W2.

W2.001

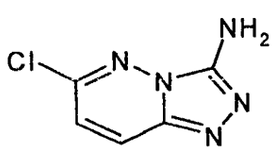
6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide



3-(Chlorpyridazin-6-yl)hydrazine (5 g) was dissolved in a mixture of EtOH (90 ml) and water (36 ml) at RT while stirring. Thereafter, 5 M cyanogen bromide solution (13 ml in acetonitrile) was cautiously added dropwise. After stirring for 4.5 h, the mixture was left to stand overnight and, the next day, further 5 M cyanogen bromide solution (3 ml in acetonitrile) was added while stirring. After a further 4 h of stirring, the precipitate formed was filtered off with suction and dried. 6.1 g of the title compound were obtained.
The mother liquor was admixed with MtB ether and the precipitate formed was filtered off with suction and dried, so as to obtain a further 1.5 g of the title compound.
LC-MS rt: 0.24 min $[M+H]^+$: 170.1 (met. a)

W2.001a

6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

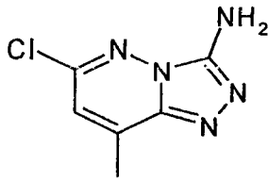


6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.001; 1.1 g) was taken up with a large amount of water and alkalized with saturated potassium carbonate solution. The solid which precipitated out was filtered off with suction and dried (388 mg). Repeated extraction of the mother liquor with dichloromethane, drying of the combined organic phases

over sodium sulfate, filtration and concentration afforded a further 228 mg of product in total.
LC-MS rt: 0.24 min $[M+H]^+$: 170.1 (met. a)

W2.002

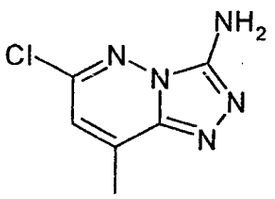
6-Chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide



(6-Chloro-4-methylpyridazin-3-yl)hydrazine (W3.002; 4.6 g) were initially charged in EtOH (330 ml) and water (70 ml) while stirring at RT. Thereafter, cyanogen bromide in a mixture of EtOH (170 ml) and water (30 ml) was slowly added dropwise at RT. After stirring at RT for 6 h, the mixture was left to stand overnight. Then the mixture was dried and the residue was purified using silica gel (40 g cartridge, DCM/methanol gradient of 0-10% in 30 min). 7.3 g of the title compound were obtained.
LC-MS rt: 0.17 min $[M+H]^+$: 184.1 (met. b)

W2.002b

6-Chloro-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine trifluoroacetic acid salt

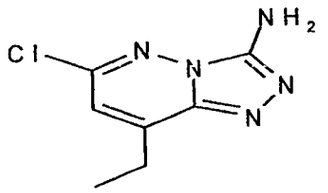


(6-Chloro-4-methylpyridazin-3-yl)hydrazine (W3.002; 432 mg) was initially charged in a mixture of ethanol (15 ml) and water (3 ml) while stirring at RT. Thereafter, cyanogen bromide (581 mg, dissolved in 7 ml of EtOH and 1.5 ml of water) was cautiously added dropwise. After stirring for 2 h, the mixture was left to stand overnight. Thereafter, the mixture was stirred at RT for a further 4 h and then at 50°C for 2 h. After cooling overnight, the solvent was drawn off and the residue was purified by means of preparative HPLC (met. A). The clean product fractions were combined, freed of the acetonitrile under reduced pressure and freeze-dried. 158 mg of the title compound were obtained.

LC-MS rt: 0.44 min $[M+H]^+$: 184.1 (met. a)

W2.003

6-Chloro-8-ethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

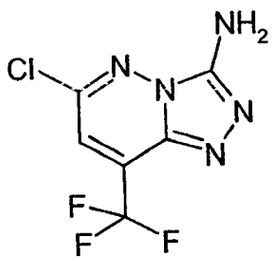


(6-Chloro-4-ethylpyridazin-3-yl)hydrazine trifluoroacetate (W3.003; 1.35 g) were initially charged in EtOH (25 ml) and water (4 ml) while stirring at RT. Thereafter, cyanogen bromide (997 mg), dissolved in EtOH/water (5/2 ml), was cautiously added dropwise. After stirring at RT for 8 h and standing overnight, the mixture was stirred at 55°C for another 4 h. Subsequently, the solvent was concentrated and the residue was admixed with water. Once it had been alkalized with saturated potassium carbonate solution, the mixture was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 918 mg of the title compound were obtained.

LC-MS rt: 0.35 min $[M+H]^+$: 198.1 (met. b)

W2.004

6-Chloro-8-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

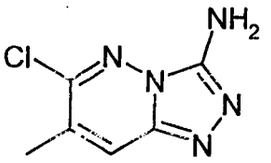


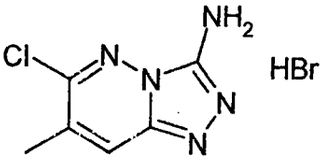
(6-Chloro-4-trifluoromethylpyridazin-3-yl)hydrazine hydrochloride (W3.004; 85 mg) was converted and worked up analogously to W2.003. However, the mixture was stirred at RT for 8 h and then left to stand over the weekend to complete the reaction.

LC-MS rt: 0.41 min $[M+H]^+$: 238.1 (met. b)

W2.005 and W2.005a

6-Chloro-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine and 6-chloro-7-methyl-[1,2,4]-triazolo[4,3-b]pyridazin-3-ylamine hydrobromide



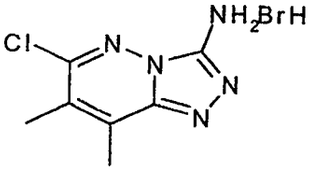


(6-Chloro-5-methylpyridazin-3-yl)hydrazine (W3.005; 4.68 g) was converted and worked up analogously to W2.002. The purification was effected using silica gel (80 g cartridge, DCM/methanol gradient 0-10% within 60 min). 1.88 g of the free base were isolated. Rinsing the silica gel again afforded 2.67 g of the hydrobromide.

LC-MS rt: 0.46 min $[M+H]^+$: 184.1 (met. a)

W2.006

6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide

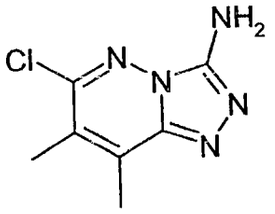


(6-Chloro-4,5-dimethylpyridazin-3-yl)hydrazine (W3.006; 12 g) was initially charged in EtOH (240 ml) and water (50 ml) while stirring at RT. Thereafter, cyanogen bromide (14.7 g) in a mixture of EtOH (120 ml) and water (25 ml) was slowly added dropwise at RT. After stirring at RT for 6 h, the mixture was left to stand overnight. Then the mixture was dried and the residue was purified using silica gel (80 g cartridge, DCM/methanol gradient of 0-20% in 60 min). 19.4 g of the title compound were obtained.

LC-MS rt: 0.28 min $[M+H]^+$: 198.1 (met. b)

W2.006a

6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

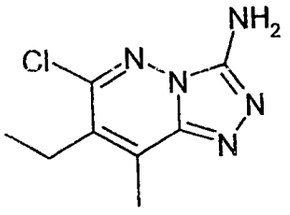


(6-Chloro-4,5-dimethylpyridazin-3-yl)hydrazine (W3.006; 519 mg) was converted and worked up analogously to W2.007. 570 mg of the free base were isolated.

LC-MS rt: 1.35 min $[M+H]^+$: 198.0 (met. e)

W2.007

6-Chloro-7-ethyl-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

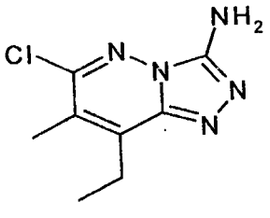


(6-Chloro-5-ethyl-4-methylpyridazin-3-yl)hydrazine (W3.007; 340 mg) was dissolved in ethanol/water (10/2 ml) at RT while stirring. Thereafter, cyanogen bromide (386 mg, dissolved in 5 ml of ethanol and 1 ml of water) was cautiously added dropwise. After stirring at RT for 5 h, the mixture was left to stand overnight and then the solvent was drawn off, and the residue was admixed with water. Once the residue had been alkalized with saturated potassium carbonate solution, it was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after filtering off the desiccant, dried under reduced pressure. 385 mg of the title compound were obtained.

LC-MS rt: 0.62 min $[M+H]^+$: 212.1 (met. b)

W2.008

6-Chloro-8-ethyl-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

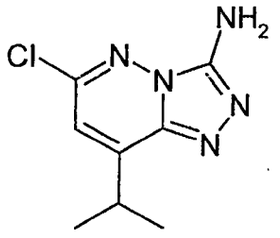


(6-Chloro-4-ethyl-5-methylpyridazin-3-yl)hydrazine trifluoroacetic acid salt (W3.008; 340 mg) was initially charged in a mixture of EtOH (12 ml) and water (2 ml) at RT while stirring. Thereafter, cyanogen bromide (240 mg), dissolved in 3 ml of EtOH and 1 ml of water, was cautiously added dropwise and the mixture was stirred for 8 h. After standing overnight, 0.5 eq. of cyanogen bromide solution was added and the mixture was stirred again at RT for 4.5 h and then at 55°C for 2 h. After standing overnight, the solvent was drawn off and the residue was admixed with water. Once it had been alkalized with saturated potassium carbonate solution, the mixture was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 270 mg of the title compound were obtained.

LC-MS rt: 0.54 min $[M+H]^+$: 212.1 (met. b)

W2.009

6-Chloro-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



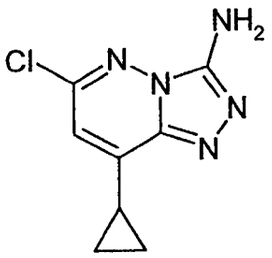
(6-Chloro-4-isopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt (W3.009; 258 mg) was initially charged in ethanol/water (6/1 ml) at RT while stirring. Thereafter, cyanogen bromide (182 mg, dissolved in a mixture of 1.5 ml of EtOH and 0.5 ml of water) was cautiously added dropwise. After stirring for 5 hours, the mixture was left to stand overnight, another 1 eq. of the cyanogen bromide solution was added and the mixture was stirred all day. After standing overnight, the solvent was drawn off and the residue was admixed with water. Once the residue had been alkalized with saturated potassium carbonate solution, it was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after filtering off the desiccant, dried under reduced pressure. 180 mg of the title compound were obtained in sufficient purity.

LC-MS rt: 0.65 min $[M+H]^+$: 212.1 (met. b)

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 6.98 (1 H), 6.63 (2 H), 3.37 (1 H), 1.35 (6 H)

W2.010

6-Chloro-8-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



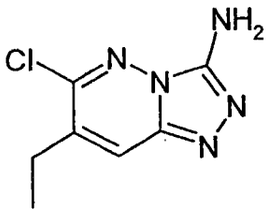
(6-Chloro-4-cyclopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt (W3.010; 400 mg) was converted and worked up analogously to W2.009. However, one further equivalent of cyanogen bromide was added and the mixture was additionally stirred at 55°C for 6 h.

252 mg of the title compound were obtained.

LC-MS rt: 0.51 min $[M+H]^+$: 210.1 (met. b)

W2.011

6-Chloro-7-ethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

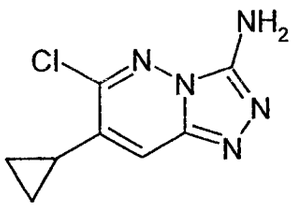


(6-Chloro-5-ethylpyridazin-3-yl)hydrazine trifluoroacetic acid salt (W3.011; 169 mg) was converted and worked up analogously to W2.009. 130 mg of the title compound were obtained in sufficient purity.

LC-MS rt: 0.33 min $[M+H]^+$: 198.1 (met. b)

W2.012

6-Chloro-7-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

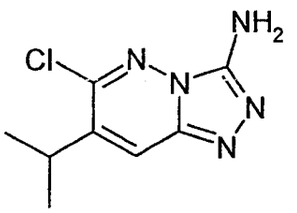


(6-Chloro-5-cyclopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt (W3.012; 400 mg) was converted and worked up analogously to W2.008, except that, instead of 0.5, one further equivalent of cyanogen bromide solution was added. 260 mg of the title compound were obtained in sufficient purity.

LC-MS rt: 0.45 min $[M+H]^+$: 210.1 (met. b)

W2.013

6-Chloro-7-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



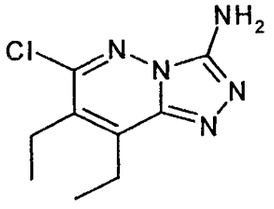
(6-Chloro-5-isopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt (W3.013; 400 mg) was initially charged in ethanol/water (6/1 ml) at RT while stirring. Thereafter, cyanogen bromide (353 mg, dissolved in a mixture of 1 ml of EtOH and 0.5 ml of water) was cautiously added dropwise. After stirring for 5 hours, the mixture was left to stand overnight and stirred for a further day. After standing overnight, the solvent was drawn off and the residue was admixed with water. Once the residue had been alkalized with saturated potassium carbonate solution, it was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after filtering off the desiccant, dried under reduced pressure. 400 mg of the title compound were obtained in sufficient purity.

LC-MS rt: 0.65 min $[M+H]^+$: 212.1 (met. b)

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.97 (1 H), 6.61 (2 H), 3.11 (1 H), 1.25 (6 H)

W2.014

6-Chloro-7,8-diethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

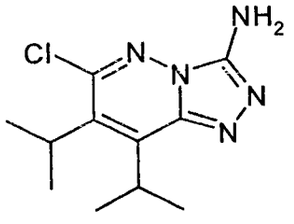


(6-Chloro-4,5-diethylpyridazin-3-yl)hydrazine (W3.014; 2.0 g) was converted and worked up analogously to W2.007. 2.20 g of the title compound were obtained in sufficient purity.

LC-MS rt: 0.72 min $[M+H]^+$: 226.1 (met. b)

W2.015

6-Chloro-7,8-diisopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

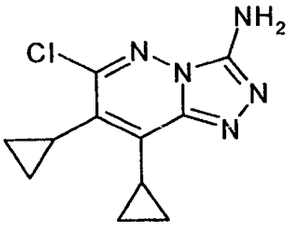


(6-Chloro-4,5-diisopropylpyridazin-3-yl)hydrazine (W3.015; 274 mg) was converted and worked up analogously to W2.007. 290 mg of the title compound were obtained in sufficient purity.

LC-MS rt: 0.87 min $[M+H]^+$: 254.2 (met. b)

W2.016

6-Chloro-7,8-dicyclopropyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

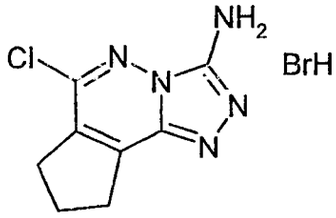


(6-Chloro-4,5-dicyclopropylpyridazin-3-yl)hydrazine (W3.016; 346 mg) was converted and worked up analogously to W2.007. 385 mg of the title compound were obtained in sufficient purity.

LC-MS rt: 0.81 min $[M+H]^+$: 250.1 (met. b)

W2.017

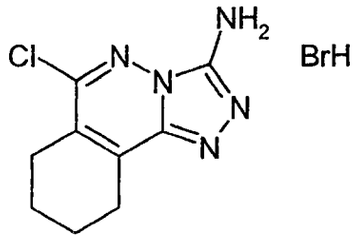
6-Chloro-8,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide



(4-Chloro-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)hydrazine (W3.017; 3.85 g) was converted, worked up and purified analogously to W2.006. 5.44 g of the title compound were obtained. LC-MS rt: 0.74 min $[M+H]^+$: 210.1 (met. a)

W2.018

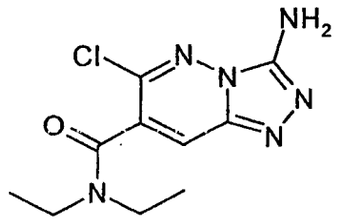
6-Chloro-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazin-3-ylamine hydrobromide



(4-Chloro-5,6,7,8-tetrahydrophthalazin-1-yl)hydrazine (W3.018; 4.00 g) was converted, worked up and purified analogously to W2.006. 5.16 g of the title compound were obtained. LC-MS rt: 0.82 min $[M+H]^+$: 224.1 (met. a)

W2.019

N,N-Diethyl-3-amino-6-chloro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide



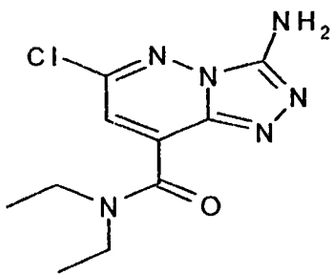
N,N-Diethyl-3-chloro-6-hydrazinopyridazine-4-carboxamide trifluoroacetic acid salt (W3.019; 390 mg) was converted and worked up analogously to W2.007. 285 mg of the title

compound were obtained in sufficient purity.

LC-MS rt: 0.94 min $[M+H]^+$: 269.1 (met. a)

W2.020

N,N-Diethyl-3-amino-6-chloro-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxamide

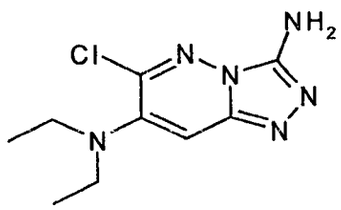


N,N-Diethyl-6-chloro-3-hydrazinopyridazine-4-carboxamide trifluoroacetic acid salt (W3.020; 320 mg) was converted and worked up analogously to W2.007. 222 mg of the title compound were obtained in sufficient purity.

LC-MS rt: 0.93 min $[M+H]^+$: 269.1 (met. a)

W2.021

6-Chloro-N*7*,N*7*-diethyl-[1,2,4]triazolo[4,3-b]pyridazine-3,7-diamine

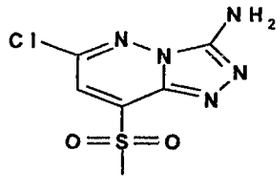


(3-Chloro-6-hydrazinopyridazin-4-yl)diethylamine (W3.021; 215 mg) was converted analogously to W2.007, and the solvent mixture was drawn off. The residue was purified by means of preparative HPLC (met. A). The product fractions, each of them clean, were combined, freed of the acetonitrile under reduced pressure, adjusted to pH 9 with sodium hydrogencarbonate and extracted five times with DCM. The combined organic phases were dried over magnesium sulfate and, after filtering off the desiccant, dried under reduced pressure. 94 mg of the title compound were obtained in sufficient purity.

LC-MS rt: 1.04 min $[M+H]^+$: 241.1 (met. a)

W2.126

6-Chloro-8-methanesulfonyl-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine

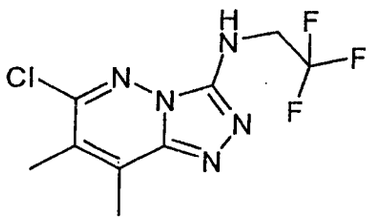


(6-Chloro-4-methanesulfonylpyridazin-3-yl)hydrazine (W3.126; 200 mg, 0.9 mmol) was dissolved in methanol (5 ml), cyanogen bromide (360 µl, 3 M in DCM) was added and the mixture was stirred at RT for 4 h. The mixture was concentrated and the residue was purified by flash chromatography (dichloromethane:methanol). Yield: 111 mg.

LC-MS rt: 0.51 min $[M+H]^+$: 227.0 (met. c)

W2.150

(6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)-(2,2,2-trifluoroethyl)amine

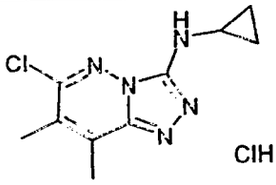
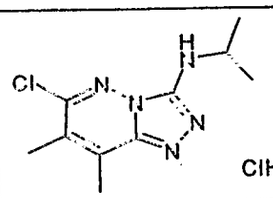
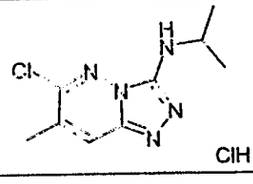


N*-(6-Chloro-4,5-dimethylpyridazin-3-yl)amino-N-(2,2,2-trifluoroethyl)urea (W3.150; 400 mg) was dissolved in phosphorus oxychloride (10 ml) and heated to 80°C while stirring. After stirring at 80°C for 7 h, the mixture was left to stand overnight and then the phosphorus oxychloride was drawn off. The residue was dissolved in water/DCM and adjusted to pH 9 with sodium hydrogencarbonate, and the phases were separated. The aqueous phase was extracted three times with DCM, and the combined extracts were washed with saturated sodium chloride solution, dried over sodium carbonate, filtered and concentrated. 330 mg of the title compound were obtained.

LC-MS rt: 0.83 min $[M+H]^+$: 280.1 (met. b)

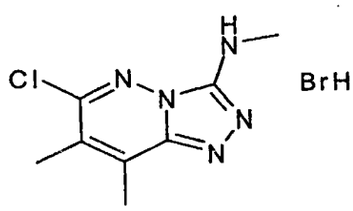
W2.166

The following were prepared analogously to W2.169:

Number		LC-MS rt	$[M+H]^+$	Comment:
W2.166		0.64 min	238.1 (met. b)	W3.166: 830 mg; purification by means of HPLC (met. D); product: 690 mg
W2.167		0.71 min	240.2 (met. b)	W3.168: 540 mg; purification by means of HPLC (met. D); product: 507 mg
W2.168		0.68 min	226.1 (met. b)	W3.168: 140 mg; purification by means of HPLC (met. D); product: 82 mg

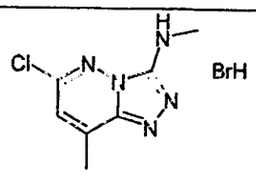
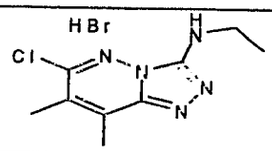
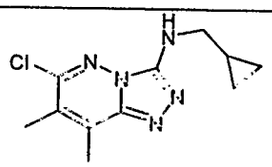
W2.169

(6-Chloro-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamine hydrobromide



N'-(6-Chloro-4,5-dimethylpyridazin-3-yl)amino-N-methylthiourea (W3.169; 11.25 g) was dissolved in ethanol (400 ml), admixed with ethyl bromoacetate (5.57 ml) and kept under reflux with exclusion of moisture. After 2 h, the solvent was drawn off and the residue was purified using silica gel (120 g cartridge, DCM/methanol gradient of 0-10% in 60 min). 10.9 g of the title compound were obtained. LC-MS rt: 0.35 min $[M+H]^+$: 212.1 (met. b)

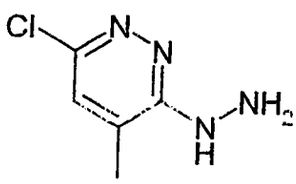
The following were prepared analogously to W2.169:

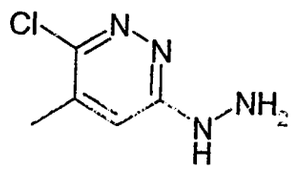
Number		LC-MS rt	$[M+H]^+$	Comment:
W2.170		0.24 min	198.1 (met. b)	W3.170: 7.74 g; product: 7.93 g
W2.191		0.50 min	226.1 (met. b)	W3.191: 7.61 g; product: 7.89 g
W2.192		0.60 min	252.1 (met. b)	W3.192: 7.80 g; product: 9.44 g

W3

W3.002

(6-Chloro-4-methylpyridazin-3-yl)hydrazine



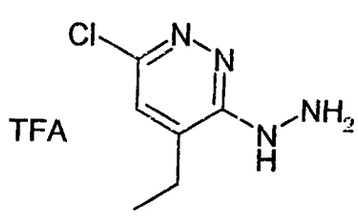


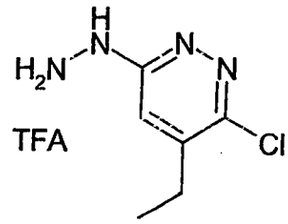
Synthesized analogously to US 4,578,464

LC-MS rt: 0.21 min $[M+H]^+$: 159.1 (met. a)

W3.003 and W3.011

(6-Chloro-4-ethylpyridazin-3-yl)hydrazine trifluoroacetate and (6-chloro-5-ethylpyridazin-3-yl)hydrazine trifluoroacetate





3,6-Dichloro-4-ethylpyridazine (W4.003, 2 x 2.4 g) was divided between 2 microwave

vessels and each was admixed with a mixture of hydrazine monohydrate (6 ml) and dioxane (7 ml). The reaction mixture was kept in the microwave at 130°C for 1 h. Subsequently, the contents of the two vessels were combined in a round-bottom flask and dried. The residue was admixed with water and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. The workup process was repeated twice more. The residue thus obtained was separated by means of preparative HPLC (method A, except gradient of 100 % water+0.05%TFA → 15% acetonitrile/85 % water+0.05%TFA in 25 min). The product fractions, each of them clean, were combined, freed of the acetonitrile under reduced pressure and freeze-dried. 1.35 g of (6-chloro-4-ethylpyridazin-3-yl)hydrazine as the trifluoroacetate and 3.96 g of (6-chloro-5-ethylpyridazin-3-yl)hydrazine as the trifluoroacetate were obtained.

(6-Chloro-4-ethylpyridazin-3-yl)hydrazine as the trifluoroacetate, W3.003

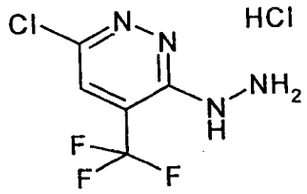
LC-MS rt: 0.20 min $[M+H]^+$: 173.1 (met. c)

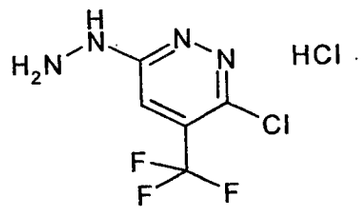
(6-Chloro-5-ethylpyridazin-3-yl)hydrazine as the trifluoroacetate, W3.011

LC-MS rt: 0.13 min $[M+H]^+$: 173.1 (met. b)

W3.004 and W3.100

(6-Chloro-4-trifluoromethylpyridazin-3-yl)hydrazine hydrochloride and (6-chloro-5-trifluoromethylpyridazin-3-yl)hydrazine hydrochloride





3,6-Dichloro-4-trifluoromethylpyridazine (W4.004, 150 mg) was dissolved in dioxane (3 ml) and, after hydrazine monohydrate (100 µl) had been added, stirred at RT. After 4 h, the solvent was drawn off and the residue was dissolved in water/ACN and separated by means of preparative HPLC (met. D). The fractions, each of them clean, were combined, freed of the acetonitrile and freeze-dried. 87 mg of (6-chloro-4-trifluoromethylpyridazin-3-yl)hydrazine hydrochloride and 7 mg of (6-chloro-5-trifluoromethylpyridazin-3-yl)hydrazine

hydrochloride were obtained.

(6-Chloro-4-trifluoromethylpyridazin-3-yl)hydrazine hydrochloride, W3.004

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (NHs not listed): 8.27 (1 H)

LC-MS rt: 0.15 min $[M+H]^+$: 213.1 (met. b)

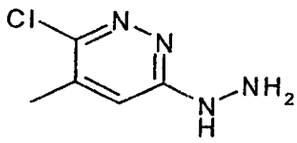
(6-Chloro-5-trifluoromethylpyridazin-3-yl)hydrazine hydrochloride, W3.100

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (NHs not listed): 7.73 (1 H)

LC-MS rt: 0.37 min $[M+H]^+$: 173.1 (met. c)

W3.005

(6-Chloro-5-methylpyridazin-3-yl)hydrazine

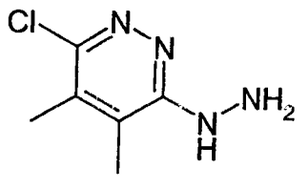


Synthesized analogously to US 4,578,464

LC-MS rt: 0.26 min $[M+H]^+$: 159.1 (met. a)

W3.006

(6-Chloro-4,5-dimethylpyridazin-3-yl)hydrazine

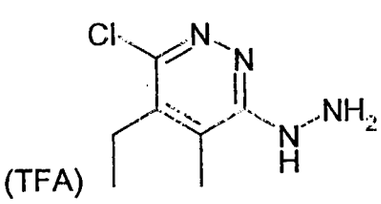


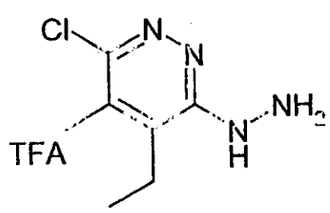
3,6-Dichloro-4,5-dimethylpyridazine (W4.006; 29.0 g) was admixed with 160ml of hydrazine monohydrate solution (160 ml) and heated to 90°C while stirring for 4 h. The reaction mixture was admixed with water and the precipitate was filtered off with suction, washed with water and dried over phosphorus pentoxide. 27.2 g of the title compound were obtained.

LC-MS rt: 0.15 min $[M+H]^+$: 173.1 (met. b)

W3.007 and W3.008

(6-Chloro-5-ethyl-4-methylpyridazin-3-yl)hydrazine (also as the TFA salt) and (6-chloro-4-ethyl-5-methylpyridazin-3-yl)hydrazine trifluoroacetic acid salt





3,6-Dichloro-4-ethyl-5-methylpyridazine (W4.007; 1 g) was initially charged in dioxane (8 ml) with addition of hydrazine monohydrate (2 ml) in a microwave vessel at RT. Thereafter, the reaction mixture was kept at 140°C in the microwave for 1 h. In the course of standing overnight, a solid precipitated out, which was filtered off with suction, washed and dried. 345 mg of (6-chloro-5-ethyl-4-methylpyridazin-3-yl)hydrazine were obtained as the free base.

The mother liquor was concentrated to dryness and the residue was purified by means of preparative HPLC (met. F). The product fractions, each of them clean, were combined, freed of the acetonitrile under reduced pressure and freeze-dried. 340 mg of 6-chloro-4-ethyl-5-methylpyridazin-3-yl)hydrazine trifluoroacetic acid salt and 239 mg of (6-chloro-5-ethyl-4-methylpyridazin-3-yl)hydrazine as the trifluoroacetate were obtained.

(6-Chloro-5-ethyl-4-methylpyridazin-3-yl)hydrazine trifluoroacetic acid salt, W3.007

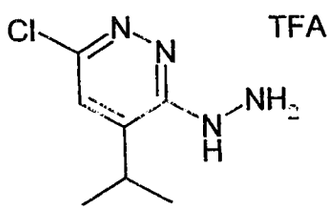
LC-MS rt: 0.25 min $[M+H]^+$: 187.1 (met. b)

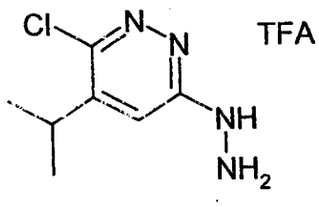
6-Chloro-4-ethyl-5-methylpyridazin-3-yl)hydrazine trifluoroacetic acid salt, W3.008

LC-MS rt: 0.22 min $[M+H]^+$: 187.1 (met. b)

W3.009 and W3.012

(6-Chloro-4-isopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt and (6-chloro-5-isopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt





3,6-Dichloro-4-isopropylpyridazine (W4.009; 2.3 g) was converted analogously to W3.007 and then dried. After preparative chromatography (met. F), 260 mg of (6-chloro-4-isopropyl-

pyridazin-3-yl)hydrazine trifluoroacetic acid salt and 2.16 g of (6-chloro-5-isopropyl-pyridazin-3-yl)hydrazine trifluoroacetic acid salt were obtained.

(6-Chloro-4-isopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt, W3.009

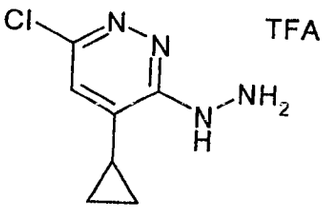
LC-MS rt: 0.20 min $[M+H]^+$: 187.1 (met. b)

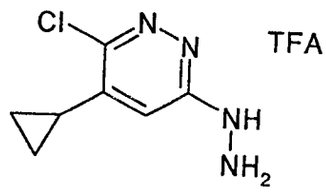
(6-Chloro-5-isopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt, W3.012

LC-MS rt: 0.34 min $[M+H]^+$: 187.1 (met. b)

W3.010 and W3.012

(6-Chloro-4-cyclopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt and (6-chloro-5-cyclopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt





3,6-Dichloro-4-cyclopropylpyridazine (W4.010; 1.4 g) was converted analogously to W3.007 and then dried. After preparative chromatography (met. F), 805 mg of (6-chloro-4-cyclopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt and 708 mg of (6-chloro-5-cyclopropylpyridazin-3-yl)hydrazine were obtained.

(6-Chloro-4-cyclopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt, W3.010

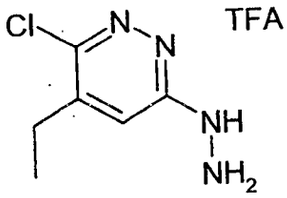
LC-MS rt: 0.15 min $[M+H]^+$: 185.1 (met. b)

(6-Chloro-5-cyclopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt, W3.012

LC-MS rt: 0.22 min $[M+H]^+$: 185.1 (met. b)

W3.011

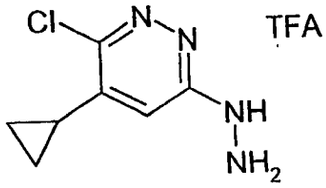
(6-Chloro-5-ethylpyridazin-3-yl)hydrazine trifluoroacetic acid salt



See W3.003

W3.012

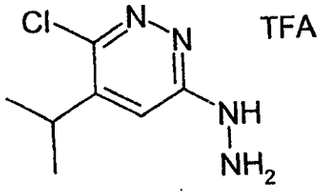
(6-Chloro-5-cyclopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt



See W3.010

W3.013

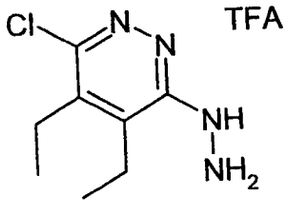
(6-Chloro-5-isopropylpyridazin-3-yl)hydrazine trifluoroacetic acid salt



See W3.009

W3.014

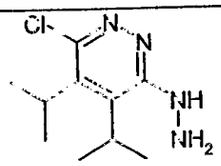
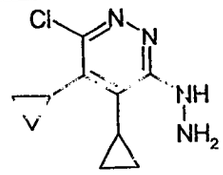
(6-Chloro-4,5-diethylpyridazin-3-yl)hydrazine trifluoroacetic acid salt



3,6-Dichloro-4,5-diethylpyridazine (W4.014; 3,0 g) was converted analogously to W3.007 and then dried. After preparative chromatography (met. F), 2.0 g of the title compound were obtained.

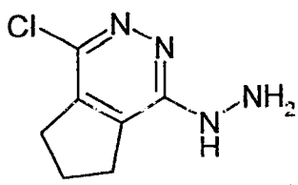
LC-MS rt: 0.38 min $[M+H]^+$: 201.1 (met. b)

Analogously to W3.007, the following were prepared:

Number		LC-MS rt	$[M+H]^+$	Comment:
W3.015		0.76 min	229.2 (met. b)	W4.015: 300 mg; 6 h MW; no HPLC purification necessary; product: 278 mg
W3.016		0.65 min	225.1 (met. b)	W4.016: 500 mg; HPLC (met. B); basified with potassium carbonate and extracted; product: 352 mg

W3.017

(4-Chloro-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)hydrazine

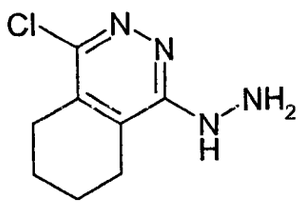


1,4-Dichloro-6,7-dihydro-5H-cyclopenta[d]pyridazine (W4.017; 3,89 g) was converted, worked up and isolated analogously to W3.006. 3.24 g of the title compound were obtained.

LC-MS rt: 0.20 min $[M+H]^+$: 185.1 (met. b)

W3.018

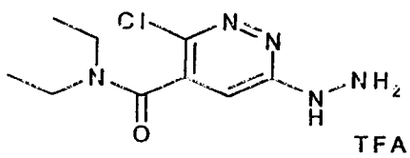
(4-Chloro-5,6,7,8-tetrahydrophthalazin-1-yl)hydrazine

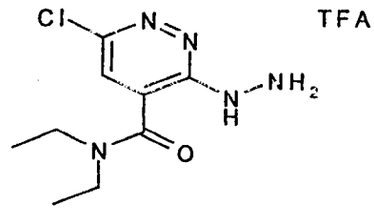


1,4-Dichloro-5,6,7,8-tetrahydrophthalazine (W4.018; 10.3 g) was converted analogously to W3.006. After water had been added, however, the mixture was extracted with DCM, and the DCM phase was removed, dried, filtered and concentrated. 9.1 g of the title compound were obtained. LC-MS rt: 0.68 min $[M+H]^+$: 199.1 (met. a)

W3.019 and W3.020

N,N-Diethyl-3-chloro-6-hydrazinopyridazine-4-carboxamide trifluoroacetic acid salt and N,N-diethyl-6-chloro-3-hydrazinopyridazine-4-carboxamide trifluoroacetic acid salt





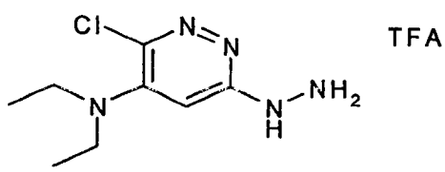
N,N-Diethyl-3,6-dichloropyridazine-4-carboxamide (W4.019; 18 g) was suspended in water (60 ml) and admixed with hydrazine monohydrate (2.8 ml). After stirring at 60°C for 1 h, the mixture was heated to 100°C for 2 h. After cooling to RT, the mixture was admixed with DCM and extracted four times with DCM. The combined extracts were dried over sodium sulfate, filtered and concentrated. The residue was purified by means of preparative HPLC (met. C). The clean, product-containing fractions were each combined, freed of ACN and freeze-dried. 910 mg of N,N-diethyl-3-chloro-6-hydrazinopyridazine-4-carboxamide trifluoroacetic acid salt and 560 mg of N,N-diethyl-6-chloro-3-hydrazinopyridazine-4-carboxamide trifluoroacetic acid salt were obtained.

N,N-Diethyl-3-chloro-6-hydrazinopyridazine-4-carboxamide trifluoroacetic acid salt
LC-MS rt: 0.79 min $[M+H]^+$: 244.1 (met. a)

N,N-Diethyl-6-chloro-3-hydrazinopyridazine-4-carboxamide trifluoroacetic acid salt
LC-MS rt: 0.68 min $[M+H]^+$: 244.1 (met. a)

W3.021

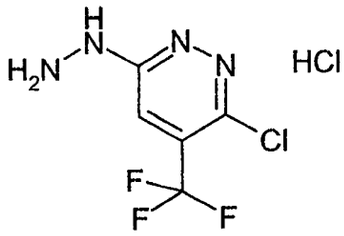
(3-Chloro-6-hydrazinopyridazin-4-yl)diethylamine trifluoroacetic acid salt



(3,6-Dichloropyridazin-4-yl)diethylamine (W4.021; 500 mg) was initially charged in dioxane (20 ml) while stirring, and admixed with hydrazine hydrate (0.65 ml). Thereafter, the mixture was heated first at 80°C for 2 h and then to reflux for 3 h. After being left to stand over the

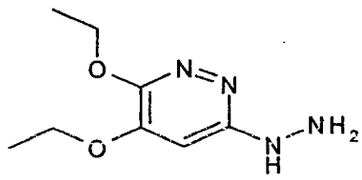
weekend, the mixture was heated to reflux for a further 48 h and, after cooling, the solvent was drawn off. The residue was purified by means of preparative HPLC (met. A). The clean, product-containing fractions were each combined, freed of the ACN, basified with saturated sodium hydrogencarbonate solution and then extracted five times with EA and five times with DCM. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. 118 mg of reactant and 220 mg of the title compound were isolated.
LC-MS rt: 1.24 min $[M+H]^+$: 220.1 (met. a)

W3.100
(6-Chloro-5-trifluoromethylpyridazin-3-yl)hydrazine hydrochloride



See W3.004

W3.120
(5,6-Diethoxypyridazin-3-yl)hydrazine



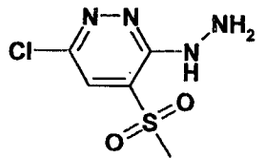
N-(5,6-Diethoxypyridazin-3-yl)-N-nitroamine (W4.120; 114 mg) was dissolved in acetic acid (5 ml) and added dropwise while cooling with ice and stirring at between 10 and 20°C to a mixture of zinc (130 mg) in water (3 ml). Thereafter, the ice bath was removed and the mixture was stirred at RT for 1 h. Then the mixture was alkalized with 10 N sodium hydroxide solution, the aqueous phase was extracted three times with DCM, and the combined DCM phases were dried over sodium sulfate, filtered and concentrated. The residue was purified by means of preparative HPLC (met. A). The clean, product-containing fractions were each combined, freed of the ACN, basified with saturated potassium carbonate solution and then extracted three times with DCM. The combined organic phases were dried

over sodium sulfate, filtered and concentrated. 50 mg of the title compound were obtained.

LC-MS rt: 0.37 min $[M+H]^+$: 199.2 (met. b)

W3.126

(6-Chloro-4-methanesulfonylpyridazin-3-yl)hydrazine

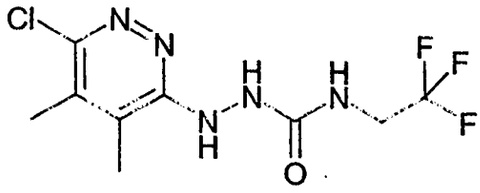


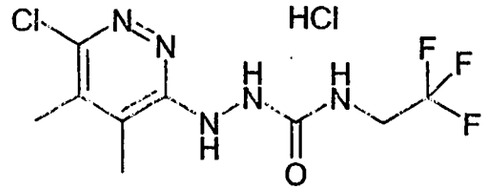
3,6-Dichloro-4-methanesulfonylpyridazine(W4.126; 660 mg, 2.9 mmol) was dissolved in 1,4-dioxane (5 ml) and hydrazine hydrate (295 µl, 5.8 mmol) was added. The mixture was stirred at RT for 4 h, then concentrated, and the residue was purified by flash chromatography (dichloromethane:ethyl acetate). Yield: 200 mg

LC-MS rt: 0.17 min $[M+H]^+$: 248.0 (met.c)

W3.150

N*-(6-Chloro-4,5-dimethylpyridazin-3-yl)amino-N-(2,2,2-trifluoroethyl)urea and N*-(6-chloro-4,5-dimethylpyridazin-3-yl)amino-N-(2,2,2-trifluorethyl)urea hydrochloride





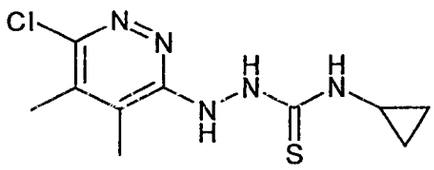
4-Nitrophenyl chloroformate (750 mg) was dissolved in THF (55 ml), 2,2,2-trifluoroethylamine (0.3 ml) was added while stirring and the mixture was stirred at RT for 3 h. Then (6-chloro-4,5-dimethylpyridazin-3-yl)hydrazine (W3.006, 620 mg) was added dissolved in THF (100 ml), followed by triethylamine (0.7 ml), and stirred at RT for 3 h. After being left to stand overnight, the precipitated solid was filtered off with suction and dried. 840 mg of the free base were obtained, which still contained significant amounts of triethylamine hydrochloride.

The mother liquor was dried and purified by means of preparative HPLC (met. D). The clean, product-containing fractions were combined and dried. A further 400 mg of the title compound were obtained as the hydrochloride.

LC-MS rt: 0.40 min $[M+H]^+$: 298.1 (met. b)

W3.166

N*-(6-Chloro-4,5-dimethylpyridazin-3-yl)amino-N-(cyclopropyl)thiourea

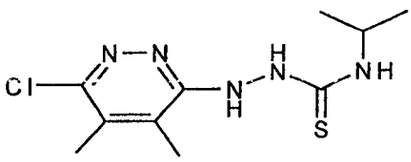


(6-Chloro-4,5-dimethylpyridazin-3-yl)hydrazine (W3.006, 540 mg) was dissolved in methylene chloride (50 ml), and cyclopropyl isothiocyanate (290 µl) was added while stirring. The mixture was stirred at RT for 7 h and then left to stand overnight. Thereafter, it was admixed with diethyl ether (50 ml) and stirred for 3 h, and the precipitate formed was filtered off with suction. The precipitate was washed with ether and dried under reduced pressure. 830 mg of the title compound were obtained.

LC-MS rt: 0.62 min $[M+H]^+$: 272.1 (met. b)

W3.167

N*-(6-Chloro-4,5-dimethylpyridazin-3-yl)amino-N-(isopropyl)thiourea

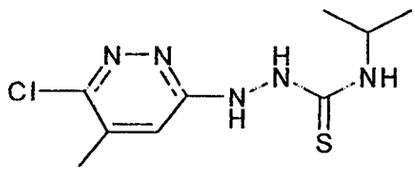


(6-Chloro-4,5-dimethylpyridazin-3-yl)hydrazine (W3.006, 380 mg) was reacted with isopropyl isothiocyanate (235 µl) and worked up analogously to W3.166. The precipitate obtained was 428 mg. The mother liquor was dried and purified using silica gel (70 g cartridge, DCM/methanol gradient 0-30% within 30 min). This afforded a further 119 mg of product.

LC-MS rt: 0.78 min $[M+H]^+$: 274.1 (met. b)

W3.168

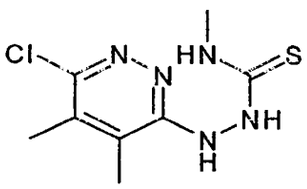
N*-(6-Chloro-5-methylpyridazin-3-yl)amino-N-(isopropyl)thiourea



6-Chloro-5-dimethylpyridazin-3-yl)hydrazine as the trifluoroacetic acid salt (W3.005, 660 mg) was dissolved in DCM (55 ml) while stirring with isopropyl isothiocyanate (258 µl) and triethylamine (310 ml) was added. Workup and isolation were effected analogously to the method described in W3.167. In this case, 140 mg of the title compound were isolated as a precipitate. LC-MS rt: 0.81 min $[M+H]^+$: 260.1 (met. b)

W3.169

N'-(6-Chloro-4,5-dimethylpyridazin-3-yl)amino-N-methylthiourea

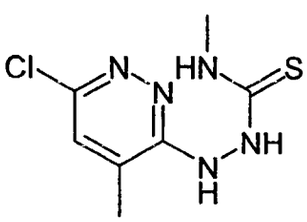


(6-Chloro-4,5-dimethylpyridazin-3-yl)hydrazine (W3.006; 8.00 g) was dissolved in DCM (400 ml) and admixed with methyl isothiocyanate (3.39 g). Subsequently, the mixture was stirred at RT for 24 h and left to stand over the weekend. The precipitate was filtered off, washed with DCM and dried in a drying cabinet at 45°C. 11.25 g of the title compound were obtained.

LC-MS rt: 0.29 min $[M+H]^+$: 246.1 (met. b)

W3.170

N'-(6-Chloro-4-methylpyridazin-3-yl)amino-N-methylthiourea

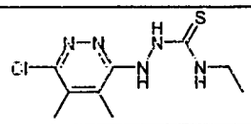
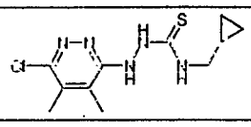


(6-Chloro-4-methylpyridazin-3-yl)hydrazine (W3.002; 5.5 g) was reacted and worked up analogously to W3.169. However, stirring was carried out for three days instead of one.

7.75 g of the title compound were obtained.

LC-MS rt: 0.20 min [M+H]$^+$: 232.1 (met. b)

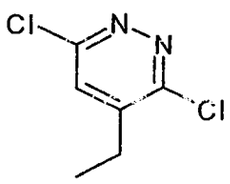
Analogously to W3.169, the following were prepared:

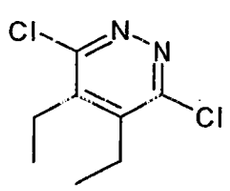
Number		LC-MS rt	[M+H]$^+$	Comment:
W3.191		0.50 min	260.0 (met. b)	W3.006: 5 g; product: 7.6 g
W3.192		0.64 min	286.0 (met. b)	W3.006: 5.0 g; product: 7.8 g

W4

W4.003 and W4.014

3,6-Dichloro-4-ethylpyridazine and 3,6-dichloro-4,5-diethylpyridazine





In analogy to: Samaritoni, Org. Prep. Proc. Int. 117 (1988)

3,6-Dichloropyridazine (10 g), silver nitrate (5.7 g) and propionic acid (7.5 ml) were initially charged in water (125 ml) and, at 50°C, concentrated sulfuric acid (11 ml) was added dropwise. After the addition, the reaction mixture was heated to 60°C and a solution of ammonium persulfate (46 g) in water (125 ml) was slowly added dropwise within 20 min. After the addition, the mixture was heated to 70°C for 30 min. After standing overnight, the reaction mixture was poured onto ice/water and adjusted to pH7 with 25% ammonium hydroxide solution. Then the mixture was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. The residue was purified by means of preparative HPLC (met. C). The product fractions, each of them clean, were combined, freed of the acetonitrile under reduced pressure and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 6.6 g of 3,6-dichloro-4-ethylpyridazine and 3.0 g of

3,6-dichloro-4,5-diethylpyridazine were obtained.

3,6-Dichloro-4-ethylpyridazine, W4.003

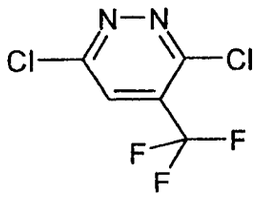
LC-MS rt: 0.83 min [M+H]$^+$: 177.1 (met. b)

3,6-Dichloro-4,5-diethylpyridazine, W4.014

LC-MS rt: 1.02 min [M+H]$^+$: 205.1 (met. b)

W4.004

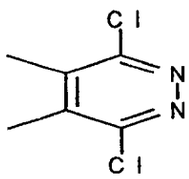
3,6-Dichloro-4-trifluoromethylpyridazine



4-Trifluoromethyl-1,2-dihydropyridazin-3,6-dione (W5.004; 125 mg) was initially charged in phosphorus oxychloride (2 ml) as a suspension while stirring at RT. Thereafter, the reaction mixture was heated to 80°C for 7 h, then phosphorus pentachloride (100 mg) was added and the mixture was stirred at 80°C overnight. After cooling, the mixture was added to ice-water and the aqueous phase was extracted three times with DCM. The combined organic phases were dried over sodium sulfate and, after filtering off the desiccant, dried under reduced pressure. 150 mg of the title compound were obtained. LC-MS rt: 0.94 min [M+H]$^+$: 217.1 (met. b)

W4.006

3,6-Dichloro-4,5-dimethylpyridazine

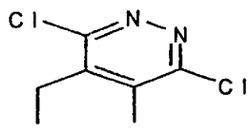


4,5-Dimethyl-1,2-dihydropyridazine-3,6-dione (W5.006; 69.7 g) was suspended in phosphorus oxychloride (150 ml) and heated to 80°C for 2 h. After cooling, the mixture was added to ice-water and adjusted cautiously to pH 10 with 10 M NaOH while cooling with ice.

The precipitate was filtered off with suction, washed with water and dried. 78.3 g of the title compound were obtained. LC-MS rt: 0.63 min $[M+H]^+$: 177.1 (met. b)

W4.007

3,6-Dichloro-4-ethyl-5-methylpyridazine

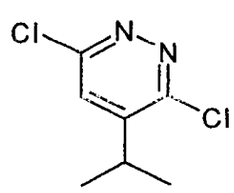


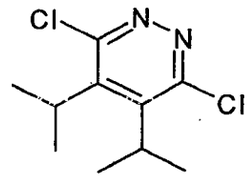
The compound was synthesized analogously to W4.003. The reactant used was 3,6-dichloro-4-methylpyridazine (4 g). 3.6 g of the title compound were obtained.

LC-MS rt: 0.92 min $[M+H]^+$: 191.1 (met. b)

W4.009 and W4.015

3,6-Dichloro-4-isopropylpyridazine and 3,6-dichloro-4,5-diisopropylpyridazine





The compound was synthesized analogously to W4.003. 2.5 g of 3,6-dichloropyridazine and isobutyric acid (2.34 ml) were used to obtain 2.46 g of 3,6-dichloro-4-isopropylpyridazine and 0.33 g of 3,6-dichloro-4,5-diisopropylpyridazine.

3,6-Dichloro-4-isopropylpyridazine, W4.009

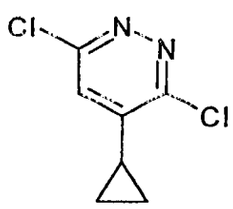
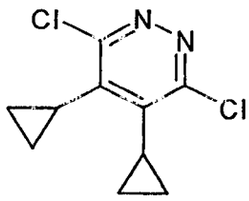
LC-MS rt: 0.96 min $[M+H]^+$: 191.1 (met. b)

3,6-Dichloro-4,5-diisopropylpyridazine, W4.015

LC-MS rt: 1.14 min $[M+H]^+$: 233.1 (met. b)

W4.010 and W4.016

3,6-Dichloro-4-cyclopropylpyridazine and 3,6-dichloro-4,5-dicyclopropylpyridazine

The compound was synthesized analogously to W4.003. 3 g of 3,6-dichloropyridazine and cyclopropanecarboxylic acid (2.41 ml) were used to obtain 1.6 g of 3,6-dichloro-4-cyclopropylpyridazine and 0.96 g of 3,6-dichloro-4,5-dicyclopropylpyridazine.

3,6-Dichloro-4-cyclopropylpyridazine, W4.010

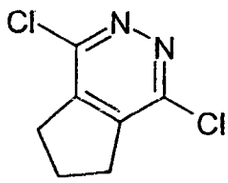
LC-MS rt: 0.87 min $[M+H]^+$: 189.1 (met. b)

3,6-Dichloro-4,5-dicyclopropylpyridazine, W4.016

LC-MS rt: 1.05 min $[M+H]^+$: 229.1 (met. b)

W4.017

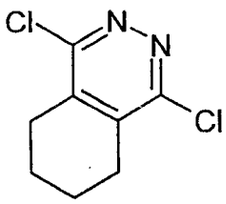
1,4-Dichloro-6,7-dihydro-5H-cyclopenta[d]pyridazine



2,3,6,7-Tetrahydro-5H-cyclopenta[d]pyridazin-1,4-dione (W5.017; 11.3 g) was suspended in phosphorus oxychloride (36.7 ml) and heated to 80°C for 2 h. After cooling, the mixture was added to ice-water and adjusted cautiously to pH 10 with 10 M NaOH while cooling with ice, and the water phase was extracted three times with EA. The combined EA phases were dried, filtered and concentrated. 3.89 g of the title compound were obtained. LC-MS rt: 0.71 min $[M+H]^+$: 189.1 (met. b)

W4.018

1,4-Dichloro-5,6,7,8-tetrahydrophthalazine

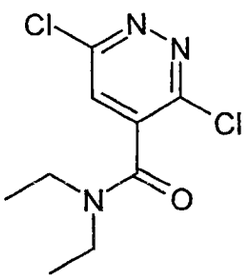


2,3,5,6,7,8-Hexahydrophthalazine-1,4-dione (W5.018; 10.1 g) was prepared analogously to W4.006. However, the precipitate was subsequently purified using silica gel (300 g, n-heptane/EA 7:3). 10.32 g of the title compound were obtained.

LC-MS rt: 1.29 min $[M+H]^+$: 203.1 (met. a)

W4.019

N,N-Diethyl-3,6-dichloropyridazine-4-carboxamide

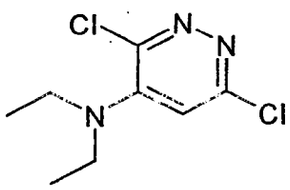


3,6-Dichloropyridazine-4-carbonyl chloride (2.5 g) was initially charged in DCM (25 ml) at RT. Thereafter, diethylamine (1.5 ml) predissolved in DCM (5 ml) was slowly added dropwise while stirring. After stirring at RT for 3 h, the mixture was admixed with water and extracted three times with DCM. The combined DCM phases were dried over sodium sulfate, filtered and concentrated. The residue was purified by means of silica gel (70 g cartridge, n-heptane/EA gradient). 1.8 g of the title compound were obtained.

LC-MS rt: 0.97 min $[M+H]^+$: 248.1 (met. a)

W4.021

(3,6-Dichloropyridazin-4-yl)diethylamine



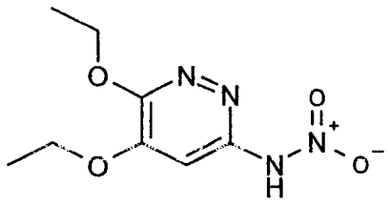
3,4,6-Trichloropyridazine (2 g) and diethylamine (2.4 ml) were initially charged in toluene

(10 ml) and left to stand at RT for 3 days. Then the mixture was admixed with water and EA, and the EA phase was removed. The EA phase was washed three times with water, dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel (70 g cartridge, n-heptane/EA gradient 0-50% within 60 min). 1.1 g of the title compound were obtained.

LC-MS rt: 1.24 min $[M+H]^+$: 248.1 (met. a)

W4.120

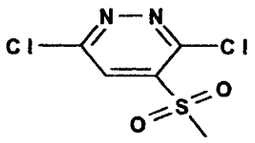
N-(5,6-Diethoxypyridazin-3-yl)-N-nitroamine



5,6-Diethoxypyridazin-3-ylamine (analogously to T. Horie in Chemical & Pharmaceutical Bulletin (1963), 11(9), 1157-67; 160 mg) was initially charged dissolved in concentrated sulfuric acid (4 ml) at RT. The mixture was then cooled to 0°C and 2 ml of a 1:1 mixture of concentrated nitric acid and concentrated sulfuric acid were added dropwise. After 20 min at 0°C, the ice bath was removed and the mixture was stirred for 4 h. Then it was cooled again to 0°C, a further 0.5 ml of the acid mixture was added and the mixture was stirred at 0°C for another hour. Then it was admixed with ice while cooling with ice. After adding DCM, the phases were separated and extracted three times with DCM. The combined DCM phases were dried over sodium sulfate, filtered and concentrated. 188 mg of the title compound were obtained. LC-MS rt: 0.81 min $[M+H]^+$: 236.2 (met. b)

W4.126

3,6-Dichloro-4-methanesulfonylpyridazine



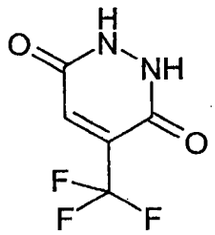
3,4,6-Trichloropyridazine (2.5 g; 13.6 mmol) and methanesulfinic acid sodium salt (2.78 g, 27.26 mmol) were stirred in 20 ml of a solvent mixture of water/THF/DMF (5:10:5) at RT for

30 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated ammonium chloride solution. The organic phase was removed and concentrated, and the crude product was purified by flash chromatography (dichloromethane:methanol). Yield: 1.4 g

LC-MS rt: 0.44 min $[M+H]^+$: 227.0 (met. b)

W5.004

4-Trifluoromethyl-1,2-dihydropyridazin-3,6-dione



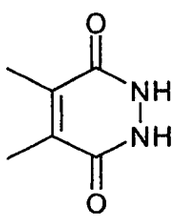
3-Trifluoromethylfuran-2,5-dione (5 g) was introduced in portions into an already boiling solution of hydrazine dihydrochloride (3.2 g) in water (50 ml). After stirring for 4 h, the mixture was left to stand overnight; the next day, the mixture was refluxed for a further 8 h and left to stand overnight. Then it was dried and the residue was purified by means of preparative chromatography (met. C). The clean fractions were combined, the ACN was drawn off and the residue was freeze-dried. 250 mg of the title compound were obtained.

LC-MS rt: 0.23 min $[M+H]^+$: 181.1 (met.b)

W5

W5.006

4,5-Dimethyl-1,2-dihydropyridazine-3,6-dione

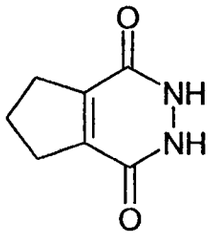


Hydrazine dihydrochloride (83.6 g) was dissolved in water (20 ml), heated to 100°C, and 3,4-dimethylfuran-2,5-dione (100.4 g) was introduced while stirring. Then the mixture was heated to reflux for 3 h. Subsequently, the precipitate formed was filtered off with suction,

washed with water and dried. The residue was suspended in EA (2 l), filtered off with suction, and was dried. 69.7 g of the title compound were obtained. LC-MS rt: 0.19 min $[M+H]^+$: 141.1 (met. b)

W5.017

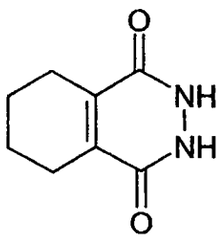
2,3,6,7-Tetrahydro-5H-cyclopenta[d]pyridazine-1,4-dione



5,6-Dihydro-4H-cyclopenta[c]furan-1,3-dione (11.3 g) was converted and worked up analogously to W5.006. Suspension in EA was not carried out. 11.3 g of crude product were obtained. LC-MS rt: 0.19 min $[M+H]^+$: 153.1 (met.b)

W5.018

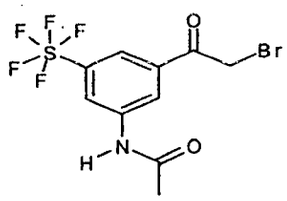
2,3,5,6,7,8-Hexahydrophthalazine-1,4-dione



2,3,5,6,7,8-Hexahydrophthalazine-1,4-dione (10.0 g) was converted analogously to W5.017. 10.14 g of the title compound were obtained.
LC-MS rt: 0.72 min $[M+H]^+$: 167.1 (met. a)

Synthesis of the units of the "eastern half"

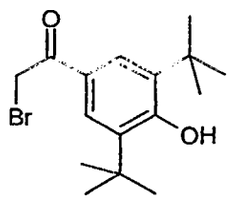
O1.001
N-[3-(2-Bromoacetyl)-5-(pentafluorosulfanyl)phenyl]acetamide



N-[3-Acetyl-5-(pentafluorosulfanyl)phenyl]acetamide (859 mg, for synthesis see example 1) was dissolved in a mixture of methanol (10 ml) and THF (10 ml) and phenyltrimethyl-ammonium tribromide (1.065 g) was added in portions while stirring. After stirring at RT for 2 h, the mixture was heated to 40°C for a further 3 h. After cooling, the reaction mixture was added to 2 N sulfuric acid and the aqueous phase was extracted 3 times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated. The crude product was purified using silica gel with ethyl acetate/heptane as the eluent. 480 mg of the desired compound were obtained. LC-MS rt: 1.47 min $[M+H]^+$: 382.0 (met. a)

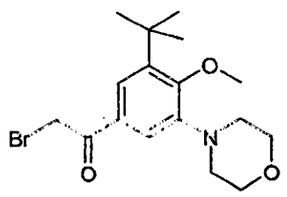
O1.002

2-Bromo-1-(3,5-di-tert-butyl-4-hydroxyphenyl)ethanone (Apollo Scientific)



O1.003

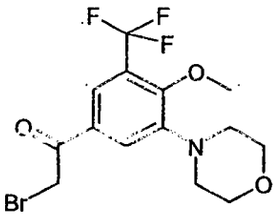
2-Bromo-1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)ethanone



Prepared as described in WO 2004/078721.

O1.004

2-Bromo-1-(4-methoxy-3-morpholin-4-yl-5-trifluoromethylphenyl)ethanone

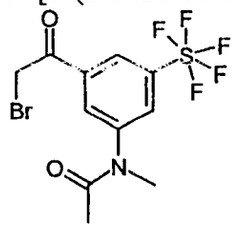


4-[5-(1,1-Dimethoxyethyl)-2-methoxy-3-trifluormethylphenyl]morpholine (O2.004; 460 mg) was dissolved in a mixture of methanol (1.4 ml) and THF (4 ml), the mixture was cooled to 7°C, and phenyltrimethylammonium tribromide (530 mg) was added in portions while stirring. After stirring at RT for 3 h, the mixture was left to stand overnight. Then aqueous thiosulfate solution (0.8 ml; w = 5 %) and water (4 ml) were added, and the mixture was admixed with EA and extracted three times with EA. The combined extracts were dried over magnesium sulfate, filtered and concentrated. The residue was dissolved in a mixture of acetonitrile (20 ml) and water (0.5 ml) and admixed with TFA (0.5 ml) while stirring. After stirring at RT for 5 h, the solvent was drawn off, and the residue was admixed with water, neutralized with saturated sodium hydrogencarbonate solution and extracted three times with ethyl acetate. The combined extracts were dried over magnesium, filtered and concentrated. The crude product was purified using silica gel with ethyl acetate/heptane as the eluent. 200 mg of the desired compound were obtained.

LC-MS rt: 1.67 min $[M+H]^+$: 382.0 (met. a)

O1.005

N-[3-(2-Bromoacetyl)-5-pentafluorosulfanylphenyl]-N-methylacetamide



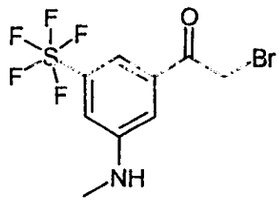
2-Bromo-1-[3-methylamino-5-(pentafluorosulfanyl)phenyl]ethanone (O1.006; 100 mg) was dissolved in DCM (5 ml) and acetyl bromide (21 µl) was added while stirring. After stirring at RT for 4 h, further acetyl bromide (21 µl) was added and the mixture was stirred further at RT. After standing overnight, the mixture was once again admixed with acetyl bromide (21 µl) and stirred for 2 h. Then the reaction mixture was concentrated and the residue was purified by means of preparative HPLC (met. A). The product fractions, each of them clean,

were combined, freed of the acetonitrile under reduced pressure, adjusted to pH 9 with sodium hydrogencarbonate solution and extracted three times with EA. The combined organic phases were dried over magnesium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 50 mg of the title compound and 18 mg of reactant were isolated.

LC-MS rt: 1.47 min $[M+H]^+$: 396.0 (met. a)

O1.006

2-Bromo-1-[3-methylamino-5-(pentafluorosulfanyl)phenyl]ethanone

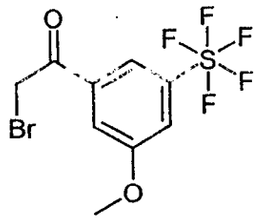


N-[3-(2-Bromoacetyl)-5-(pentafluorosulfanyl)phenyl]-2,2,2-trifluoro-N-methylacetamide (O1.075; 1.2 g) was admixed with water (15 ml), and concentrated sulfuric acid (15 ml) was added dropwise while stirring and with ice cooling. The mixture was heated to 80°C and stirred at this temperature for 7 h. After cooling, the reaction mixture was added slowly to a mixture of 10 N sodium hydroxide solution and EA, and the aqueous phase was extracted five times with EA. The combined organic phases were dried over magnesium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. The residue was purified by means of preparative HPLC (met. A). The product fractions, each of them clean, were combined, freed of the acetonitrile under reduced pressure, neutralized with sodium hydrogencarbonate and extracted three times with EA. The combined organic phases were dried over magnesium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 420 mg of the title compound were isolated.

LC-MS rt: 1.64 min $[M+H]^+$: 354.0 (met. a)

O1.007

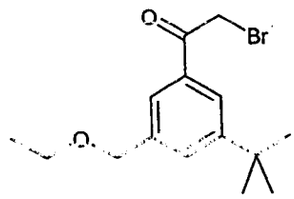
2-Bromo-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone



1-[3-Methoxy-5-(pentafluorosulfanyl)phenyl]ethanone (O2.007; 1.63 g) was dissolved in THF (150 ml), and phenyltrimethylammonium tribromide (2.2 g) was added at RT while stirring. After stirring at RT for 2 h, the mixture was admixed with water, neutralized with sodium hydrogencarbonate solution and extracted three times with EA. The alkaline water phase was extracted 3 x with EA. The combined organic phases were dried over magnesium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. The residue was purified by means of preparative HPLC (met. A). The product fractions, each of them clean, were combined, freed of the acetonitrile under reduced pressure, neutralized with sodium hydrogencarbonate and extracted three times with EA. The combined organic phases were dried over magnesium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 1.27 g of the title compound were isolated. LC-MS rt: 1.65 min $[M+H]^+$: 354.9 (met. b)

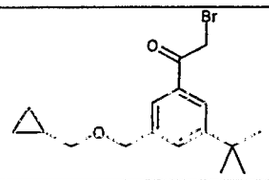
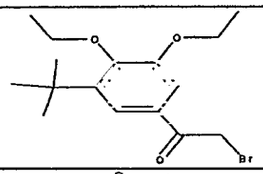
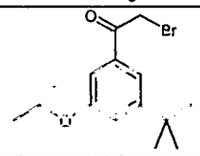
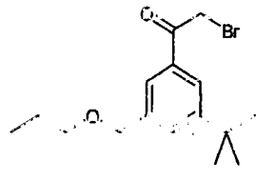
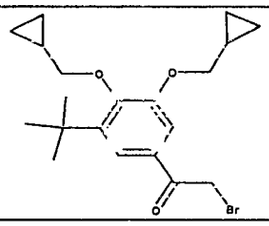
O1.008

2-Bromo-1-(3-tert-butyl-5-ethoxymethylphenyl)ethanone



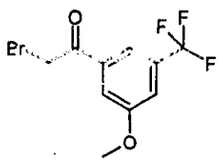
1-(3-tert-Butyl-5-ethoxymethylphenyl)ethanone (O2.008; 550 mg) was dissolved in methanol/ THF (10 ml/10 ml), admixed with phenyltrimethylammonium tribromide (882 mg) while stirring and stirred at RT for 2 h. Subsequently, the reaction mixture was poured onto DCM (200 ml) and washed thoroughly once with 5% sodium thiosulfate solution and once with water. Then the DCM phase was dried and concentrated. The residue was purified using silica gel (40 g cartridge, n-heptane/EA gradient of 0-50% in 30 min). 566 mg of the title compound were obtained. LC-MS rt: 1.83 min $[M+H]^+$: 313.2 (met. a)

The following were prepared analogously:

Number		LC-MS rt	$[M+H]^+$	Comment:
O1.009		1.92 min	339.2 (met. a)	O2.009; 595 mg; product: 691 mg
O1.010		2.01 min	343.2 (met. a)	O2.010; 410 mg; product: 405 mg
O1.011		1.77 min	299.2 (met. a)	O2.011; 390 mg; 5% citric acid solution added instead of thiosulfate; product: 387 mg
O1.012		1.94 min	327.2 (met. a)	O2.012; 333 mg; stirred at RT for 12 h; stirred with 20% citric acid solution instead of thio-sulfate solution 1 h; product: 327 mg
O1.013		2.16 min	395.3 (met. a)	O2.013; 540 mg; after thiosulfate solution, washed additionally with 20% citric acid solution; product: 600 mg

O1.014

2-Bromo-1-(3-methoxy-5-trifluoromethylphenyl)ethanone

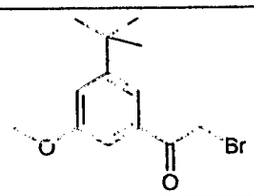
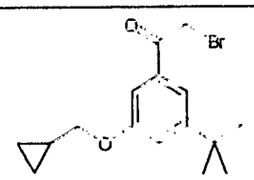
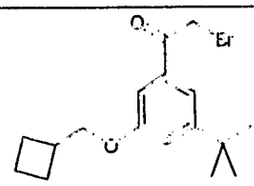
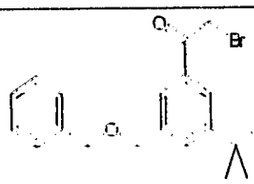
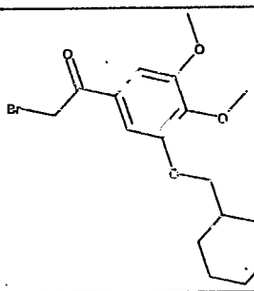


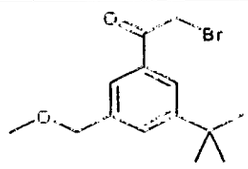
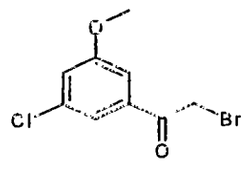
1-(3-Methoxy-5-trifluormethylphenyl)ethanone (O2.014, 50 mg) was dissolved in DCM (0.8 ml) and added dropwise at RT to a mixture of copper(II) bromide (102 mg) in EA (1.2 ml). After heating to RT for 2 h, the mixture was left to stand overnight, then the reaction mixture was filtered through "Celite" and washed thoroughly with EA, and the filtrate was dried. The residue was taken up with EA and semisaturated sodium hydrogencarbonate

solution and then extracted twice with EA. The combined EA phases were washed with semisaturated sodium hydrogencarbonate solution, dried over sodium sulfate, filtered and concentrated. The crude product was purified by means of preparative HPLC (met. A). The product fractions, each of them clean, were combined, freed of the acetonitrile under reduced pressure and extracted three times with EA. The combined organic phases were dried over sodium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 39 mg of the title compound were isolated.

LC-MS rt: 1.64 min $[M+H]^+$: 297.0 (met. a)

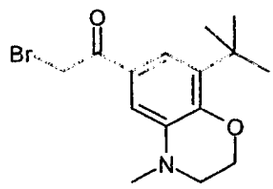
The following were prepared analogously to O1.008:

Number		LC-MS rt	$[M+H]^+$	Comment:
O1.015		1.77 min	285.1 (met. a)	O2.015: 880 mg; 5% citric acid solution added instead of thiosulfate solution; product: 327 mg
O1.016		1.97 min	325.1 (met. a)	O2.016: 1.02 g; stirred with 5% citric acid solution for 2 h instead of thiosulfate solution; product: 1.23 g
O1.017		2.14 min	339.2 (met. a)	O2.017: 25 mg; stirred with 5% citric acid solution for 2 h instead of thiosulfate solution; product: 314 mg
O1.018		2.18 min	389.3 (met. a)	O2.018: 638 mg; stirred with 5% citric acid solution for 2 h instead of thiosulfate solution; product: 809 mg
O1.019		1.94 min	371.3 (met. a)	O2.019: 360 mg; after thiosulfate solution, washed additionally with 20% citric acid solution; product: 261 mg

O1.020		1.72 min	299.1 (met. a)	O2.020: 1.53 g; after thiosulfate solution, washed additionally with 20% citric acid solution; product: 1.04 g
O1.021		1.58 min	262.9/ 265.0 (met. a)	O2.021: 41 g; after thiosulfate solution, washed additionally with 20% citric acid solution; product: 572 mg

O1.022

2-Bromo-1-(8-tert-butyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)ethanone

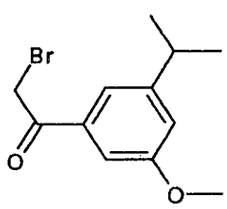


1-(8-tert-Butyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)ethanone (250 mg, purchased from Chembiotek, India) was heated to from 50°C to 55°C in a mixture of acetic acid (4 ml) and toluene (8 ml). At this temperature, bromine (200 mg dissolved in acetic acid) was cautiously added dropwise. After 2.5 h, the heating was removed, and the mixture was admixed at RT with ice-water and extracted three times with toluene. The combined organic phases were dried over sodium sulfate, filtered and concentrated. The crude product was purified using silica gel, so as to obtain 65 mg of the desired compound, as well as a further 43 mg of product which was slightly contaminated and 37 mg of reactant.

LC-MS rt: 1.81 min $[M+H]^+$: 326.0 (met. a)

O1.030

2-Bromo-1-(3-isopropyl-5-methoxyphenyl)ethanone

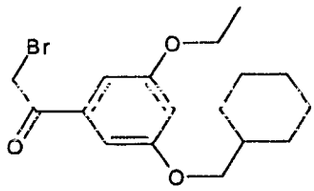


1-(3-Isopropyl-5-methoxyphenyl)ethanone (O2.030; 425 mg) was dissolved in methanol/THF

(15 ml/15 ml) and admixed while stirring with phenyltrimethylammonium tribromide (831 mg). After stirring at RT for 3 h, the reaction mixture was added to 50 ml of 20% citric acid and stirred for 1 h. After adding water and EA, the EA phase was removed, dried and concentrated. The residue was dissolved in acetonitrile (50 ml), and 2 N sulfuric acid (15 ml) was added to the solution. After standing at RT for 2 h, the mixture was admixed with water and extracted with EA. The EA phase was washed with saturated sodium hydrogencarbonate solution, dried and concentrated. The residue was purified using silica gel (40 g cartridge, n-heptane/EA gradient of 0-50% within 30 min). 520 mg of the title compound were obtained. LC-MS rt: 1.65 min $[M+H]^+$: 271.1 (met. a)

O1.031

2-Bromo-1-(3-cyclohexylmethoxy-5-ethoxyphenyl)ethanone

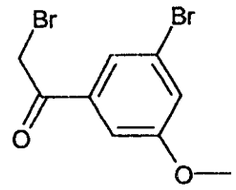


Proceeding from 1-(3-cyclohexylmethoxy-5-ethoxyphenyl)ethanone (O2.031, 1.76 g), the title compound was prepared analogously to O1.008. For further purification, however, the silica gel chromatography was followed by a further purification by means of preparative HPLC. 370 mg of the title compound were obtained.

LC-MS rt: 2.11 min $[M+H]^+$: 355.1 (met. a)

O1.032

2-Bromo-1-(3-bromo-5-methoxyphenyl)ethanone



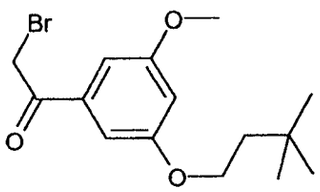
1-(3-Bromo-5-methoxyphenyl)ethanone (O2.032, 1.45 g) was dissolved in methanol/THF (40 ml/40 ml) and admixed while stirring with phenyltrimethylammonium tribromide (2.38 g). After stirring at RT for 24 h, water and EA were added. The EA phase was removed, dried and concentrated. The residue was dissolved in acetonitrile (50 ml), and 2 N

sulfuric acid (15 ml) was added to the solution. After standing at RT for 1 h, the mixture was admixed with water and extracted twice with EA. The EA phase was washed with saturated sodium hydrogencarbonate solution, dried and concentrated. The residue was purified using silica gel (40 g cartridge, n-heptane/EA gradient of 0-50% within 30 min). 1.39 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.71 (1 H), 7.48 (2 H), 4.97 (2 H), 3.84 (3 H)

O1.033

2-Bromo-1-[3-(3,3-dimethylbutoxy)-5-methoxyphenyl]ethanone

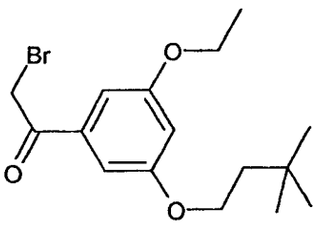


Proceeding from 1-[3-(3,3-dimethylbutoxy)-5-methoxyphenyl]ethanone (1.11 g), the title compound was prepared analogously to O1.031. 127 mg of the title compound were obtained.

LC-MS rt: 1.89 min $[M+H]^+$: 329.1 (met. a)

O1.034

2-Bromo-1-[3-(3,3-dimethylbutoxy)-5-ethoxyphenyl]ethanone

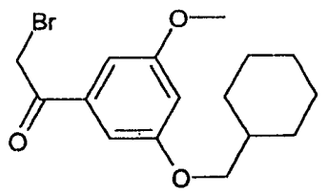


Proceeding from 1-[3-(3,3-dimethylbutoxy)-5-ethoxyphenyl]ethanone (950 mg), the title compound was prepared analogously to O1.031. 236 mg of the title compound were obtained, which was still somewhat contaminated.

LC-MS rt: 2.06 min $[M+H]^+$: 343.2 (met. a)

O1.035

2-Bromo-1-(3-cyclohexylmethoxy-5-methoxyphenyl)ethanone

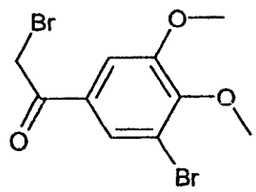


1-(3-Cyclohexylmethoxy-5-methoxyphenyl)ethanone (O2.035; 1.33 g) was converted analogously to O1.032. However, the mixture was stirred at RT only for 3 h instead of 24. 950 mg of the title compound were obtained.

LC-MS rt: 2.03 min $[M+H]^+$: 341.2 (met. a)

O1.040

2-Bromo-1-(3-bromo-4,5-dimethoxyphenyl)ethanone

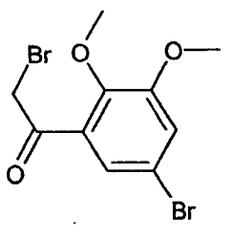


1-(3-Bromo-4,5-dimethoxyphenyl)ethanone (O2.040; 1.22 g) was converted analogously to O1.032. 1.05 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.86 (1 H), 7.58 (1 H), 4.96 (2 H), 3.90 (3 H), 3.82 (3 H)

O1.041

2-Bromo-1-(5-bromo-2,3-dimethoxyphenyl)ethanone

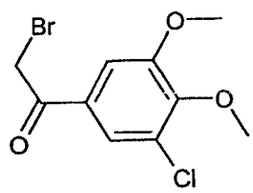


1-(5-Bromo-2,3-dimethoxyphenyl)ethanone (O2.041; 1.1 g) was converted analogously to O1.032. 1.21 g of the title compound were obtained.

LC-MS rt: 1.62 min $[M+H]^+$: 337.0 (met. a)

O1.042

2-Bromo-1-(3-chloro-4,5-dimethoxyphenyl)ethanone

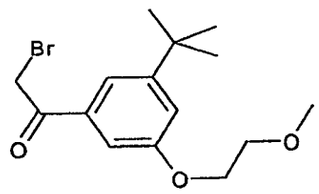


1-(3-Chloro-4,5-dimethoxyphenyl)ethanone (O2.042; 490 mg) was converted analogously to O1.032. 577 mg of the title compound were obtained.

LC-MS rt: 1.54 min $[M+H]^+$: 293.0 (met. a)

O1.043

2-Bromo-1-[3-tert-butyl-5-(2-methoxyethoxy)phenyl]ethanone

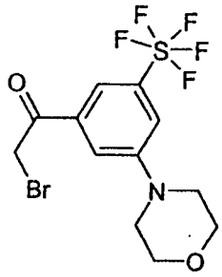


1-[3-tert-Butyl-5-(2-methoxyethoxy)phenyl]ethanone (O2.043; 1 g) was dissolved in methanol/THF (25 ml/25 ml), admixed with phenyltrimethylammonium tribromide (882 mg) while stirring and stirred at RT overnight. Then 50 ml of 20 % citric acid solution were added und the mixture was stirred for 1 h. Subsequently, DCM (200 ml) was added and the mixture was extracted three times with DCM. Then the combined DCM phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel (40 g cartridge, n-heptane/EA gradient of 0-30% in 30 min). 1.31 g of the title compound were obtained.

LC-MS rt: 1.72 min $[M+H]^+$: 329.2 (met. a)

O1.044

2-Bromo-1-[3-morpholin-4-yl-5-(pentafluorosulfanyl)phenyl]ethanone

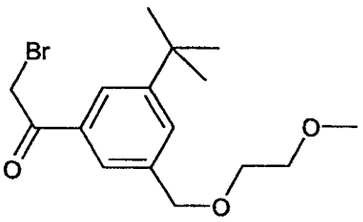


1-[3-Morpholin-4-yl-5-(pentafluorosulfanyl)phenyl]ethanone (O2.044; 1.1 g) was dissolved in methanol/THF (20/20 ml) and admixed while stirring with phenyltrimethylammonium tribromide (1.25 g). After stirring at RT for 27 h, 50 ml of 20% citric acid were added and the mixture was stirred for 1 h. After adding DCM (100 ml), the DCM phase was removed, dried and concentrated. The residue was dissolved in acetonitrile (100 ml), and 2 N sulfuric acid (20 ml) was added to the solution. After stirring at RT for 24 h, the mixture was admixed with water and extracted with EA. The EA phase was washed with saturated sodium hydrogencarbonate solution, dried and concentrated. The residue was purified using silica gel (80 g cartridge, n-heptane/EA gradient of 0-60% within 40 min). 866 mg of the title compound were obtained.

LC-MS rt: 1.69 min $[M+H]^+$: 410.0 (met. a)

O1.045

2-Bromo-1-[3-tert-butyl-5-(2-methoxyethoxymethyl)phenyl]ethanone

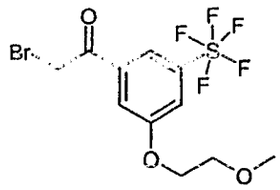


1-[3-tert-Butyl-5-(2-methoxyethoxymethyl)phenyl]ethanone (O2.045, 508 mg) was converted analogously to O1.032. 470 mg of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.91 (1 H), 7.76 (1 H), 7.66 (1 H), 4.96 (2 H), 4.56 (2 H), 3.58 (2 H), 3.50 (2 H), 3.26 (3 H), 1.32 (9 H)

O1.050

2-Bromo-1-[3-(2-methoxyethoxy)-5-(pentafluorosulfanyl)phenyl]ethanone

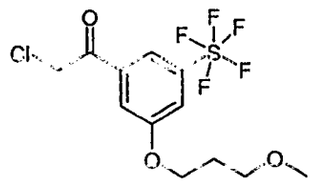


1-[3-(2-Methoxyethoxy)-5-(pentafluorosulfanyl)phenyl]ethanone (O3.050, 578 mg) was converted analogously to O1.032. 290 mg of the title compound were obtained.

LC-MS rt: 1.70 min $[M+H]^+$: 399.0 (met. a)

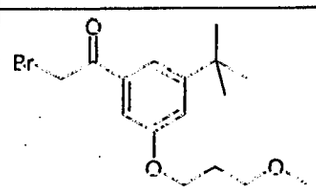
O1.051

2-Chloro-1-[3-(3-methoxypropoxy)-5-(pentafluorosulfanyl)phenyl]ethanone



1-[3-(3-Methoxypropoxy)-5-(pentafluorosulfanyl)phenyl]ethanone (O2.051; 670 mg) was dissolved in methanol/THF (10 ml/10 ml) and admixed while stirring with phenyltrimethylammonium tribromide (753 mg). After stirring at RT for 24 h, water and EA were added. The EA phase was removed, dried and concentrated. The residue was dissolved in acetonitrile (50 ml), and 2 N hydrochloric acid (15 ml) was added to the solution. After stirring at RT for 1 h, the mixture was admixed with water and extracted twice with EA. The EA phase was dried and concentrated. The residue was purified using silica gel (40 g cartridge, n-heptane/EA gradient of 0-30% in 30 min). 722 mg of the title compound were obtained, which was still contaminated by the analogous 2-bromo compound.

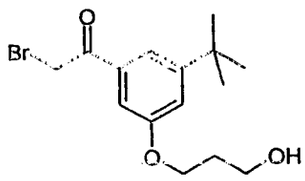
LC-MS rt: 1.11 min $[M+H]^+$: 369.0 (met. b)

Number		LC-MS rt	$[M+H]^+$	Comment:
O1.052		1,82 min	343.1 (met. a)	Synthesis analogous to O1.013: O2.052: 880 mg; chromatography: 80 g

				cartridge, n-heptane/MTB ether 0-30% within 60 min; product: 629 mg

O1.059

2-Bromo-1-[3-tert-butyl-5-(3-hydroxypropoxy)phenyl]ethanone

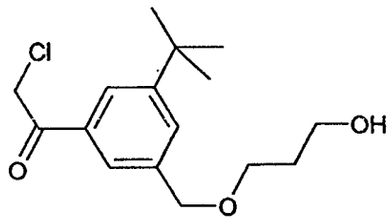


1-{3-tert-Butyl-5-[3-(tetrahydropyran-2-yloxy)propoxy]phenyl}ethanone (O2.059; 3.4 g) was dissolved in methanol/THF (50/50 ml) and admixed while stirring with phenyltrimethylammonium tribromide (4.21 g). After stirring at RT for 3 h, 20% citric acid solution was added and the mixture was stirred for 1 h. Then EA was added and the EA phase was removed. The EA phase was dried over magnesium sulfate and concentrated by rotary evaporation. The residue was purified by means of silica gel (80 g cartridge, n-heptane/EA gradient of 0-50% within 60 min). 2.49 g of the title compound were obtained.

LC-MS rt: 2.57 min $[M+H]^+$: 329.1 (met. e)

O1.060

1-[3-tert-Butyl-5-(3-hydroxypropoxymethyl)phenyl]-2-chloroethanone

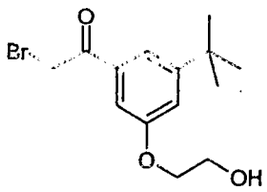


1-{3-tert-Butyl-5-[3-(tetrahydropyran-2-yloxy)propoxymethyl]phenyl}ethanone (O2.060; 1.75 g) was converted analogously to O1.063. 455 mg of the title compound were obtained.

LC-MS rt: 1.47 min $[M+H]^+$: 299.1 (met. a)

O1.061

2-Bromo-1-[3-tert-butyl-5-(2-hydroxyethoxy)phenyl]ethanone

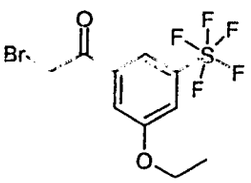


1-{3-tert-Butyl-5-[2-(tetrahydropyran-2-yloxy)ethoxy]phenyl}ethanone (O2.061; 3.9 g) was dissolved in methanol/THF (60 ml/60 ml) and admixed while stirring with phenyltrimethylammonium tribromide (5.03 g). After stirring at RT for 3 h, the reaction mixture was added to 20% citric acid and stirred for 1 h. After adding EA, the EA phase was removed, dried and concentrated. The residue was purified using silica gel (80 g cartridge, n-heptane/EA gradient of 0-50% within 60 min). 2.56 g of the title compound were obtained.

LC-MS rt: 0.90 min $[M+H]^+$: 315.0 (met. b)

O1.062

2-Bromo-1-[3-ethoxy-5-(pentafluorosulfanyl)phenyl]ethanone

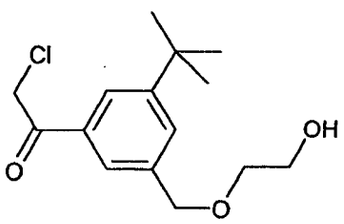


1-[3-Ethoxy-5-(pentafluorosulfanyl)phenyl]ethanone (O2.062; 2.24 g) was converted analogously to O1.008. The purification using silica gel was performed as follows: (120 g cartridge, n-heptane/MtB ether gradient of 0-20% within 60 min). 2.07 g of the title compound were obtained.

LC-MS rt: 1.83 min $[M+H]^+$: 368.9 (met. a)

O1.063

1-[3-tert-Butyl-5-(2-hydroxyethoxymethyl)phenyl]-2-chloroethanone



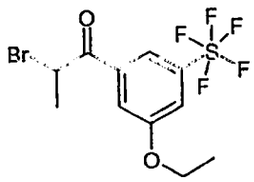
1-{3-tert-Butyl-5-[2-(tetrahydropyran-2-yloxy)ethoxymethyl]phenyl}ethanone (O2.063;

2.0 g) was dissolved in methanol/THF (30 ml/30 ml) and admixed while stirring with phenyltrimethylammonium tribromide (2.25 g). After stirring at RT for 3 h, the mixture was diluted with DCM and washed once with 5% sodium thiosulfate solution, and the DCM phase was dried over magnesium sulfate and concentrated by rotary evaporation. The residue was dissolved in THF (200 ml), and 3 N HCl (30 ml) was added. After standing for 1 h, EA and water were added, and the EA phase was removed. The EA phase was dried over magnesium sulfate and concentrated by rotary evaporation. The residue was purified using silica gel (40 g cartridge, n-heptane/EA gradient of 0-50% within 40 min). 774 mg of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.87 (1 H), 7.76 (1 H), 7.67 (1 H), 5.21 (2 H), 4.66 (1 H), 4.56 (2 H), 3.56 (2 H), 3.49 (2 H), 1.32 (9 H)

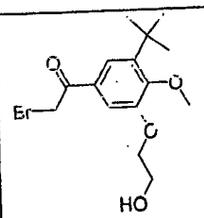
O1.064

2-Bromo-1-[3-ethoxy-5-(pentafluorosulfanyl)phenyl]propan-1-one



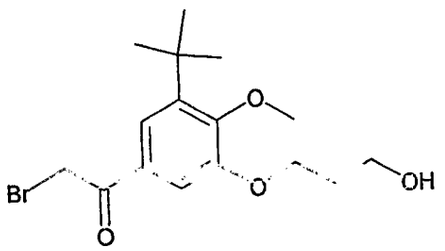
1-[3-Ethoxy-5-(pentafluorosulfanyl)phenyl]propan-1-one (O2.064; 150 mg) was dissolved in THF (15 ml), and phenyltrimethylammonium tribromide (185 mg) was added while stirring at RT. After stirring at RT for 5 h, the mixture was admixed with water and saturated sodium hydrogencarbonate solution, and EA was added. The EA phase was removed and the alkaline water phase was extracted three times with EA. The combined organic phases were washed once with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by means of preparative HPLC (met. A). The product fractions, each of them clean, were combined, freed of the acetonitrile under reduced pressure, alkalized with saturated sodium hydrogencarbonate solution and extracted five times with EA. The combined organic phases were dried over magnesium sulfate and, after filtering off the desiccant, dried under reduced pressure. 120 mg of the title compound were isolated.

LC-MS rt: 1.29 min $[M+H]^+$: 383.0 (met. b)

Number		LC-MS rt	$[M+H]^+$	Comment:
O1.070		0.96 min	345.1 (met. b)	Synthesis analogous to O1.071: O2.070: 6.68 g; product: 3.3 g

O1.071

2-Bromo-1-[3-tert-butyl-5-(3-hydroxypropoxy)-4-methoxyphenyl]ethanone

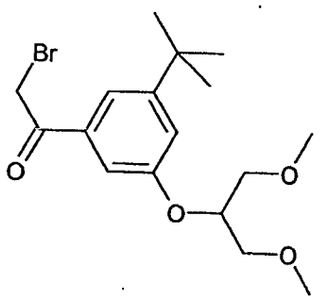


1-{3-tert-Butyl-4-methoxy-5-[3-(tetrahydropyran-2-yloxy)propoxy]phenyl}ethanone (O2.071; 12.7 g) was dissolved in methanol/THF (200/200 ml) and admixed with phenyltrimethylammonium tribromide (13.1 g) while stirring. The mixture was stirred at RT for 1 h, then diluted with DCM and washed once with 5% sodium thiosulfate solution. The DCM phase was dried over magnesium sulfate, filtered and concentrated. The residue was taken up in acetonitrile (100 ml) and admixed with 48% hydrobromic acid (5.91 ml). The mixture was left to stand for 1 h, then admixed with water, extracted by shaking with EA, and the combined EA phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel (120 g cartridge, n-heptane/MtB ether gradient of 0-100% in 60 min). 3.29 g of the title compound were obtained.

LC-MS rt: 1.01 min $[M+H]^+$: 359.1 (met. b)

O1.072

2-Bromo-1-[3-tert-butyl-5-(2-methoxy-1-methoxymethylethoxy)phenyl]ethanone

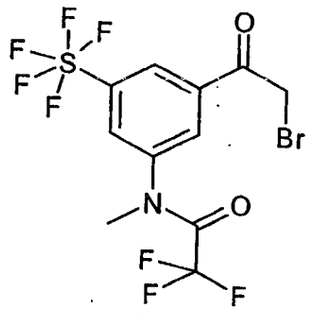


1-[3-tert-Butyl-5-(2-methoxy-1-methoxymethylethoxy)phenyl]ethanone (O2.072; 1.64 g) was dissolved in methanol/THF (30/30 ml) and admixed while stirring with phenyltrimethylammonium tribromide (2.09 g). The mixture was stirred at RT for 1 h, then diluted with DCM and washed once with 5% sodium thiosulfate solution. The DCM phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel (80 g cartridge, n-heptane/MtB ether gradient of 0-30% within 60 min). 890 mg of the title compound were obtained.

LC-MS rt: 1.77 min $[M+H]^+$: 373.0 (met. a)

O1.075

N-[3-(2-Bromoacetyl)-5-(pentafluorosulfanyl)phenyl]-2,2,2-trifluoro-N-methylacetamide



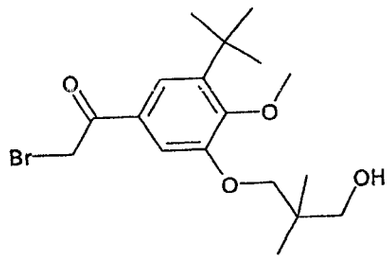
N-[3-Acetyl-5-(pentafluorosulfanyl)phenyl]-2,2,2-trifluoro-N-methylacetamide (O2.075; 1.03 g) was dissolved in a mixture of methanol (20 ml) and THF (20 ml). Phenyltrimethylammonium tribromide (1.05 g) was added while stirring. After stirring at RT for 5 h, the mixture was left to stand overnight, then further phenyltrimethylammonium tribromide (100 mg) was added and the mixture was heated to 60°C for 2 h. After cooling, the reaction mixture was added to 2 N sulfuric acid and stirred for 10 min. Then the aqueous phase was extracted three times with EA. The combined organic phases were dried over magnesium sulfate and, after the desiccant had been filtered off, dried under reduced pressure. 1.2 g of

the title compound were obtained, which had sufficient purity for the next reactions.

LC-MS rt: 1.72 min $[M+H]^+$: 449.9 (met. a)

O1.085

2-Bromo-1-[3-tert-butyl-5-(3-hydroxy-2,2-dimethylpropoxy)-4-methoxyphenyl]ethanone

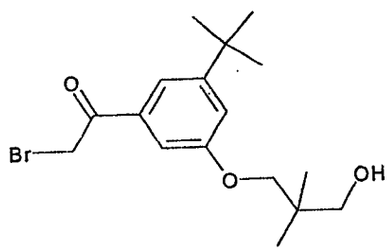


3-(5-Acetyl-3-tert-butyl-2-methoxyphenoxy)-2,2-dimethylpropyl acetate (O2.085; 1.16 g) was converted and worked up analogously to O1.008. The purification using silica gel was carried out as follows: (80 g cartridge, n-heptane/MtB ether gradient of 0-70% within 60 min). 867 mg of the title compound were obtained.

LC-MS rt: 1.80 min $[M+H]^+$: 387.1 (met. a)

O1.086

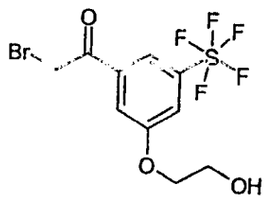
2-Bromo-1-[3-tert-butyl-5-(3-hydroxy-2,2-dimethylpropoxy)phenyl]ethanone



1-[3-tert-Butyl-5-(3-hydroxy-2,2-dimethylpropoxy)phenyl]ethanone (O2.086; 388 mg) was converted, worked up and purified analogously to O1.085. 311 mg of the title compound was obtained. LC-MS rt: 1.78 min $[M+H]^+$: 357.0 (met. a)

O1.090

2-Bromo-1-[3-(2-hydroxyethoxy)-5-(pentafluorosulfanyl)phenyl]ethanone

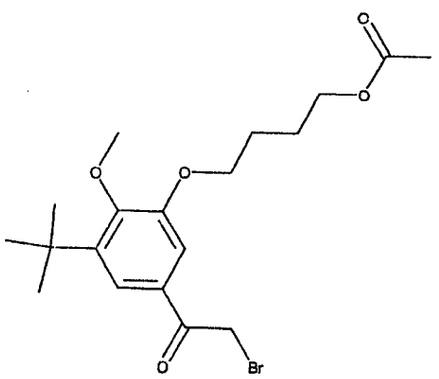


1-{3-(Pentafluorosulfanyl)-5-[2-(tetrahydropyran-2-yloxy)ethoxy]phenyl}ethanone (O2.090; 813 mg) was converted, worked up and purified analogously to O1.071. However, the reaction time was three hours instead of one. 174 mg of the title compound were obtained.

LC-MS rt: 0.94 min $[M+H]^+$: 385.0 (met. b)

O1.095

4-[5-(2-Bromoacetyl)-3-tert-butyl-2-methoxyphenoxy]butyl acetate

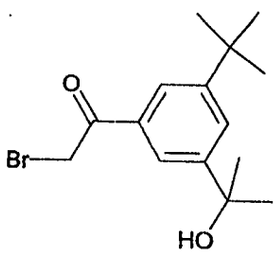


4-(5-Acetyl-3-tert-butyl-2-methoxyphenoxy)butyl acetate (O2.095; 10.51 g) was converted, worked up and purified analogously to O1.071. 4.81 g of the title compound were obtained.

LC-MS rt: 1.21 min $[M+H]^+$: 415.1 (met. b)

O1.100

2-Bromo-1-[3-tert-butyl-5-(1-hydroxy-1-methylethyl)phenyl]ethanone

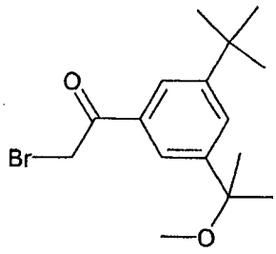


1-[3-tert-Butyl-5-(1-hydroxy-1-methylethyl)phenyl]ethanone (O2.100; 50 mg) was initially charged in THF (5 ml) while stirring at RT, and admixed with phenyltrimethylammonium

tribromide (80 mg). After stirring at RT for 3 h, the mixture was left to stand overnight and admixed with water and saturated sodium hydrogencarbonate solution. Then it was extracted three times with EA, and the combined EA phases were dried over sodium sulfate, filtered and concentrated. The residue was purified using silica gel (10 g cartridge, n-heptane/EA gradient). 42 mg of the title compound were obtained. LC-MS rt: 1.10 min $[M+H-H_2O]^+$: 295.1 (met. b)

O1.101

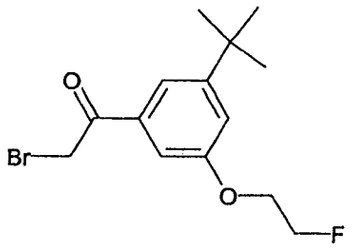
2-Bromo-1-[3-tert-butyl-5-(1-methoxy-1-methylethyl)phenyl]ethanone



1-[3-tert-Butyl-5-(1-hydroxy-1-methylethyl)phenyl]ethanone (O2.100; 500 mg) was initially charged in a mixture of THF and methanol (3.5/3.5 ml) while stirring at RT, and admixed with phenyltrimethylammonium tribromide (800 mg). After stirring at RT for 7 h, the mixture was admixed with water and saturated sodium hydrogencarbonate solution. Then it was extracted three times with EA, and the combined EA phases were dried over sodium sulfate, filtered and concentrated. The residue was purified using silica gel (70 g cartridge, n-heptane/EA gradient). 454 mg of the title compound were obtained. LC-MS rt: 1.23 min $[M+H-HOMe]^+$: 295.1 (met. b)

O1.105

2-Bromo-1-[3-tert-butyl-5-(2-fluoroethoxy)phenyl]ethanone ZSI2.063

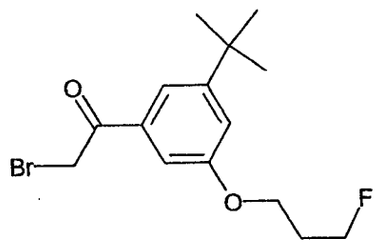


1-[3-tert-Butyl-5-(2-fluoroethoxy)phenyl]ethanone (O2.105; 600 mg) was dissolved in

methanol/THF (15/15 ml). While stirring, phenyltrimethylammonium tribromide (950 mg) was added. After stirring at RT for 3 h, water (5 ml) was added and the mixture was dried. The residue was admixed with DCM (200 ml) and saturated sodium hydrogencarbonate solution (100 ml). The DCM phase was removed and the aqueous phase was extracted three times more with DCM. The combined DCM phases were dried over sodium sulfate, filtered and concentrated. The residue was purified using silica gel (50 g cartridge, n-heptane/EA gradient of 0-60% within 40 min). 560 mg of the title compound were obtained.
LC-MS rt: 1.19 min $[M+H]^+$: 317.1 (met. b)

O1.106

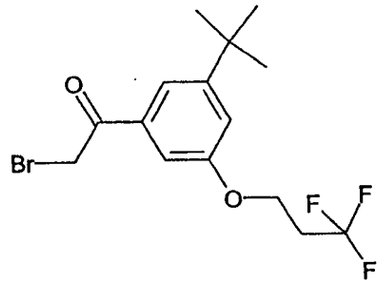
2-Bromo-1-[3-tert-butyl-5-(3-fluoropropoxy)phenyl]ethanone



1-[3-tert-Butyl-5-(3-fluoropropoxy)phenyl]ethanone (630 mg) was converted, worked up and purified analogously to O1.105. 510 mg of the title compound were obtained. LC-MS rt: 1.23 min $[M+H]^+$: 331.1 (met. b)

O1.107

2-Bromo-1-[3-tert-butyl-5-(3,3,3-trifluoropropoxy)phenyl]ethanone

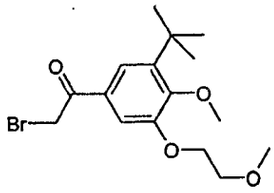


1-[3-tert-Butyl-5-(3,3,3-trifluoropropoxy)phenyl]ethanone (O2.107; 170 mg, 0.59 mmol) was dissolved in a mixture of THF (3 ml) and methanol (3 ml). While stirring, phenyltrimethylammonium tribromide (222 mg, 0.59 mmol) was introduced and the mixture was stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with saturated

sodium hydrogencarbonate solution. After drying over sodium sulfate, the solvent was removed and the residue was purified by flash chromatography (n-heptane:ethyl acetate).
Yield: 42 mg,
LC-MS rt: 1.19 min $[M+H]^+$: 367.1 (met. b)

O1.110

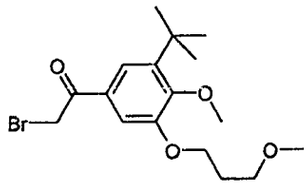
2-Bromo-1-[3-tert-butyl-4-methoxy-5-(2-methoxyethoxy)phenyl]ethanone



1-[3-tert-Butyl-4-methoxy-5-(2-methoxyethoxy)phenyl]ethanone (O2.110; 1.17 g) was converted, worked up and purified analogously to O1.008. 1.18 g of the title compound were obtained. LC-MS rt: 1.10 min $[M+H]^+$: 359.1 (met. b)

O1.111

2-Bromo-1-[3-tert-butyl-4-methoxy-5-(3-methoxypropoxy)phenyl]ethanone

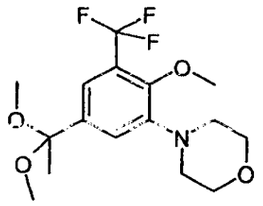


1-[3-tert-Butyl-4-methoxy-5-(3-methoxypropoxy)phenyl]ethanone (O2.111; 1.49 g) was converted, worked up and purified analogously to O1.008. 1.65 g of the title compound were obtained. LC-MS rt: 1.16 min $[M+H]^+$: 373.0 (met. b)

O2

O2.004

4-[5-(1,1-Dimethoxyethyl)-2-methoxy-3-trifluoromethylphenyl]morpholine

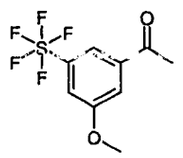


1-Bromo-5-(1,1-dimethoxyethyl)-2-methoxy-3-trifluoromethylbenzene (O3.004; 700 mg) was initially charged in dioxane (7 ml) and admixed successively with Pd(II) acetate (46 mg), cesium carbonate (2 g), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (118 mg) and morpholine (0.27 ml). Thereafter, the reaction mixture was heated to 90°C for 7 h and then left to stand overnight. Subsequently, it was filtered and the filtrate was concentrated by rotary evaporation. The residue was purified using silica gel (50 g cartridge, n-heptane/EA gradient). 433 mg of the title compound were obtained.

LC-MS rt: 1.55 min $[M+H]^+$: 304.0 (met. a)

O2.007

1-[3-Methoxy-5-(pentafluorosulfanyl)phenyl]ethanone

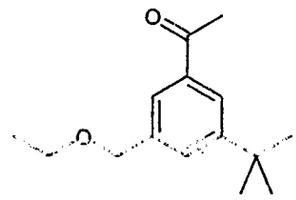


3,N-Dimethoxy-N-methyl-5-(pentafluorosulfanyl)benzamide (O3.007; 2.0 g) was dissolved in absolute THF (60 ml), and methylmagnesium bromide (5.2 ml, 3 M in diethyl ether) was added dropwise at 0°C while stirring. After addition, the ice bath was removed and the mixture was stirred at RT for 2 h. 1 N hydrochloric acid was then added dropwise while cooling, followed by water and ethyl acetate. The organic phase was removed and the aqueous phase was extracted twice more with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated. The residue was purified by means of preparative HPLC (met. A). The product-containing fractions were combined, freed of the acetonitrile and extracted three times with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated. 1.63 g of the desired compound were obtained.

^{1}H NMR (400 MHz, DMSO-d6) [ppm]: 7.87 (1 H), 7.75 (1 H), 7.67 (1 H), 3.91 (3 H), 2.64 (3 H)

O2.008

1-(3-tert-Butyl-5-ethoxymethylphenyl)ethanone

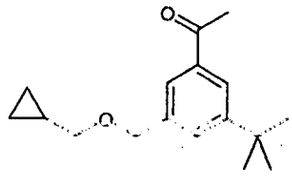


3-tert-Butyl-N-methoxy-5-methoxymethyl-N-methylbenzamide (O3.008; 854 mg) was converted analogously to O2.043. 550 mg of the title compound were obtained.

LC-MS rt: 1.70 min $[M+H]^+$: 235.3 (met. a)

O2.009

1-(3-tert-Butyl-5-cyclopropylmethoxymethylphenyl)ethanone

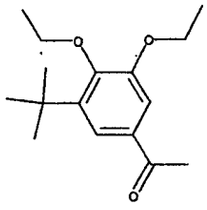


Proceeding from methyl 3-tert-butyl-5-hydroxymethylbenzoate and cyclopropylmethyl bromide, the title compound (600 mg) was prepared analogously to O5.008 to O2.008.

LC-MS rt: 1.81 min $[M+H]^+$: 261.2 (met. a)

O2.010

1-(3-tert-Butyl-4,5-diethoxyphenyl)ethanone

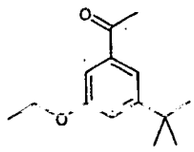


1-(3-tert-Butyl-4-ethoxy-5-hydroxyphenyl)ethanone (O3.010; 470 mg) and ethyl iodide (193 µl) were dissolved in DMF (6.2 ml), and sodium hydride (57 mg) was added. After stirring at RT for 0.5 h, the DMF was drawn off and the residue was taken up in EA, washed with water, dried and concentrated. The residue was purified using silica gel (40 g cartridge,

n-heptane/EA gradient 0-30% within 60 min). 420 mg of the title compound were obtained.
LC-MS rt: 1.93 min $[M+H]^+$: 265.2 (met. a)

O2.011

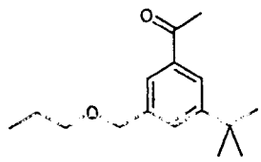
1-(3-tert-Butyl-5-ethoxyphenyl)ethanone



Methyl 3-tert-butyl-5-hydroxybenzoate (O6.043) was reacted with ethyl iodide analogously to O5.043 and converted to the title compound analogously to the sequence of O4.043 to O2.043. 390 mg were obtained.
LC-MS rt: 1.72 min $[M+H]^+$: 221.3 (met. a)

O2.012

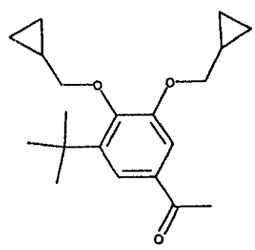
1-(3-tert-Butyl-5-propoxymethylphenyl)ethanone



Proceeding from methyl 3-tert-butyl-5-hydroxymethylbenzoate and propyl iodide, the title compound (333 mg) was prepared analogously to O5.008 to O2.008.
LC-MS rt: 1.81 min $[M+H]^+$: 261.2 (met. a)

O2.013

1-(3-tert-Butyl-4,5-bis(cyclopropylmethoxy)phenyl)ethanone

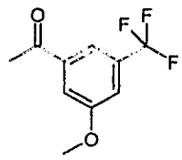


Proceeding from 2-bromo-6-tert-butyl-4-(1,1-dimethoxyethyl)phenol and cyclopropyl bromide, the title compound (547 mg) was prepared analogously to O4.010 to O2.010.

LC-MS rt: 2.10 min $[M+H]^+$: 317.4 (met. a)

O2.014

1-(3-Methoxy-5-trifluoromethylphenyl)ethanone

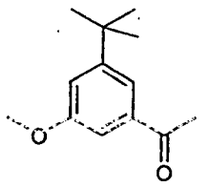


3,N-Dimethoxy-N-methyl-5-trifluoromethylbenzamide (O3.014, 460 mg) was initially charged in THF (15 ml) under at RT Ar dissolved. Thereafter, the mixture was cooled to 0°C, and methylmagnesium bromide (1.5 ml; 3 M in diethyl ether) was added dropwise. Subsequently, the ice bath was removed and the mixture was stirred at RT for 2 h. Then the mixture was admixed with 1 N hydrochloric acid while cooling with ice, diluted with water and extracted three times with EA. The combined EA phases were dried over sodium sulfate, filtered and concentrated. 349 mg of the title compound were isolated.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.80 (1 H), 7.73 (1 H), 7.53 (1 H), 3.92 (3 H), 2.66 (3 H)

O2.015

1-(3-tert-Butyl-5-methoxyphenyl)ethanone

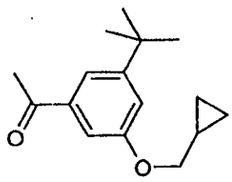


Methyl 3-tert-butyl-5-hydroxybenzoate (O6.043) was reacted with methyl iodide analogously to O5.043 and converted to the title compound analogously to the sequence O4.043 to O2.043. 880 mg were obtained.

LC-MS rt: 1.65 min $[M+H]^+$: 207.1 (met. a)

O2.016

1-(3-tert-Butyl-5-cyclopropylmethoxyphenyl)ethanone

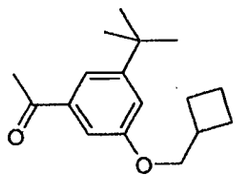


Methyl 3-tert-butyl-5-hydroxybenzoate (O6.043) was reacted with cyclopropylmethyl bromide analogously to O5.043, and converted to the title compound analogously to the sequence O4.043 to O2.043. 1.02 g were obtained.

LC-MS rt: 1.86 min $[M+H]^+$: 247.1 (met. a)

O2.017

1-(3-tert-Butyl-5-cyclobutylmethoxyphenyl)ethanone

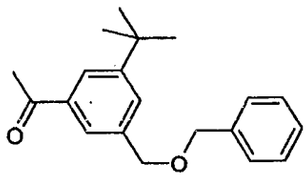


Methyl 3-tert-butyl-5-hydroxybenzoate (O6.043) was reacted with bromomethylcyclobutane analogously to O5.043 and converted to the title compound analogously to the sequence O4.043 to O2.043. 252 mg were obtained.

LC-MS rt: 2.07 min $[M+H]^+$: 261.2 (met. a)

O2.018

1-(3-Benzyloxymethyl-5-tert-butylphenyl)ethanone

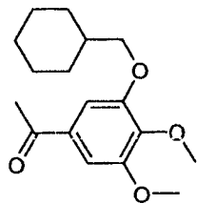


Methyl 3-tert-butyl-5-hydroxymethylbenzoate was reacted with benzyl bromide analogously to O5.043 and converted to the title compound analogously to the sequence O4.008 to O2.008. 638 mg were obtained.

LC-MS rt: 1.93 min $[M+H]^+$: 297.2 (met. a)

O2.019

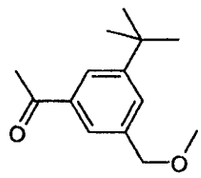
1-(3-Cyclohexylmethoxy-4,5-dimethoxyphenyl)ethanone



3-Cyclohexylmethoxy-4,5,N-trimethoxy-N-methylbenzamide (420 mg) was converted and worked up analogously to O2.059. No silica gel purification was performed. 370 mg were obtained. LC-MS rt: 1.82 min $[M+H]^+$: 293.2 (met. a)

O2.020

1-(3-tert-Butyl-5-methoxymethylphenyl)ethanone

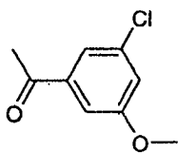


Methyl 3-tert-butyl-5-hydroxymethylbenzoate was reacted with methyl iodide analogously to O5.043, and converted to the title compound analogously to the sequence O4.008 to O2.008. 1.54 g were obtained.

LC-MS rt: 1.58 min $[M+H]^+$: 221.1 (met. a)

O2.021

1-(3-Chloro-5-methoxyphenyl)ethanone

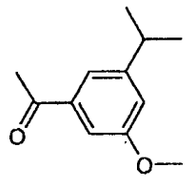


3-Chloro-5-methoxybenzoic acid (3 g) was reacted analogously to O3.043/O2.043 with thionyl chloride (23.3 ml) and N,O-dimethylhydroxylamine hydrochloride (1.57 g) and methylmagnesium bromide (8.91 ml). 2.42 g were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.54 (1 H), 7.40 (1 H), 7.30 (1 H), 3.84 (3 H), 2.58 (3 H)

O2.030

1-(3-Isopropyl-5-methoxyphenyl)ethanone

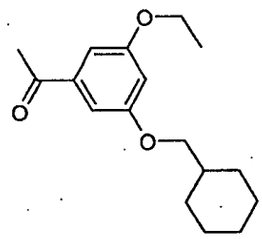


Methyl 3-hydroxy-5-isopropylbenzoate was reacted with methyl iodide analogously to O5.043 and converted to the title compound analogously to the sequence O4.043 to O2.043. 425 mg were obtained.

LC-MS rt: 1.54 min $[M+H]^+$: 193.1 (met. a)

O2.031

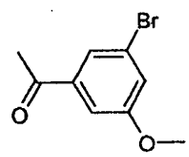
1-(3-Cyclohexylmethoxy-5-ethoxyphenyl)ethanone



1-(3,5-Dihydroxyphenyl)ethanone (1.0 g) and ethyl bromide (0.531 ml) were dissolved at RT in DMF (20 ml), and sodium hydride (189 mg) was added. After stirring at 50°C for 2 h, cyclohexylmethyl bromide (1.36 ml) was added, followed by further sodium hydride (315 mg). After stirring at 50°C for another 2 h, the DMF was drawn off and the residue was taken up in EA, washed with water, dried, filtered and concentrated. The residue was purified using silica gel (80 g cartridge, n-heptane/EA gradient of 0-20% within 60 min). 378 mg of the title compound were obtained. LC-MS rt: 2.07 min $[M+H]^+$: 277.2 (met. a)

O2.032

1-(3-Bromo-5-methoxyphenyl)ethanone



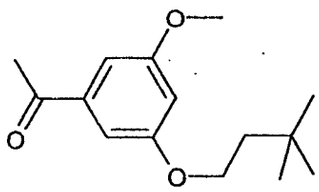
Methyl 3-bromo-5-methoxybenzoate (O5.032; 2.50 g) was converted to the title compound

analogously to the sequence O4.043, O3.043 and O2.059. 1.45 g were obtained.

LC-MS rt: 1.46 min $[M+H]^+$: 229.0 (met. a)

O2.033

1-[3-(3,3-Dimethylbutoxy)-5-methoxyphenyl]ethanone

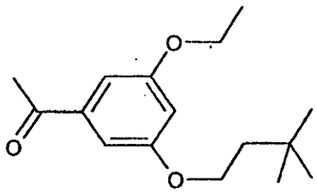


1-(3-Hydroxy-5-methoxyphenyl)ethanone (O3.033; 1.12 g) and 1-iodo-3,3-dimethylbutane (1.57 g) were dissolved in DMF, and sodium hydride (194 mg) was added. After stirring at RT for 2 h, the DMF was drawn off. The residue was taken up in EA, washed with water, dried, filtered and concentrated. The residue was purified using silica gel (40 g cartridge, n-heptane/EA 0-50% within 30 min). 850 mg of the title compound were obtained.

LC-MS rt: 1.83 min $[M+H]^+$: 251.1 (met. a)

O2.034

1-[3-(3,3-Dimethylbutoxy)-5-ethoxyphenyl]ethanone

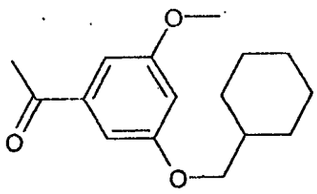


1-(3,5-Dihydroxyphenyl)ethanone (3.0 g) was converted analogously to O2.031. Instead of cyclohexylbromide, however, 1-bromo-3,3-dimethylbutane was used. After chromatography, 960 mg of the title compound were obtained.

LC-MS rt: 1.99 min $[M+H]^+$: 265.2 (met. a)

O2.035

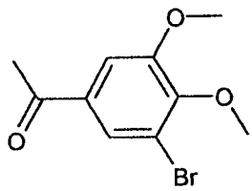
1-(3-Cyclohexylmethoxy-5-methoxyphenyl)ethanone



1-(3-Hydroxy-5-methoxyphenyl)ethanone (O3.033; 1.5 g) and bromomethylcyclohexane (1.76 g) were dissolved in DMF (20 ml), and sodium hydride (260 mg) was added. After stirring at 50°C for 24 h, the DMF was drawn off. The residue was taken up in EA, washed with water, dried, filtered and concentrated. The residue was purified using silica gel (40 g cartridge, n-heptane/EA 0-50% within 30 min). 1.33 g of the title compound were obtained.
LC-MS rt: 1.93 min $[M+H]^+$: 263.2 (met. a)

O2.040

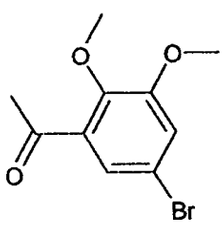
1-(3-Bromo-4,5-dimethoxyphenyl)ethanone



3-Bromo-4,5-dimethoxybenzoic acid (2.0 g) was converted to the benzamide derivative analogously to O3.043, and the latter was converted to the title compound analogously to O2.059. 1.22 g of the title compound were obtained.
^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.78 (1 H); 7.53 (1 H); 3.90 (3 H); 3.82 (3 H); 2.57 (3 H)

O2.041

1-(5-Bromo-2,3-dimethoxyphenyl)ethanone



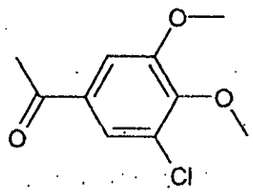
5-Bromo-2,3-dimethoxybenzoic acid (2 g) was converted to the benzamide derivative analogously to O3.043, and the latter to the title compound analogously to O2.059. 1.1 g of

the title compound were obtained.

LC-MS rt: 3.70 min $[M+H]^+$: 259.0 (met. d)

O2.042

1-(3-Chloro-4,5-dimethoxyphenyl)ethanone

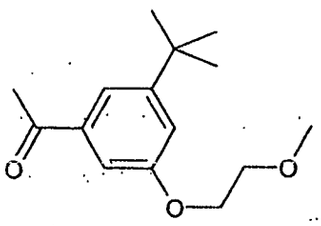


3-Chloro-4,5-dimethoxybenzoic acid (1 g) was converted to the benzamide derivative analogously to O3.043, and the latter to the title compound analogously to O2.059. 495 mg of the title compound were obtained.

LC-MS rt: 1.55 min $[M+H]^+$: 215.1 (met. a)

O2.043

1-[3-tert-Butyl-5-(2-methoxyethoxy)phenyl]ethanone

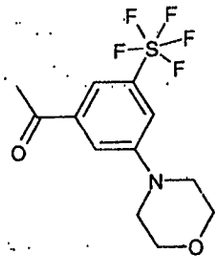


3-tert-Butyl-N-methoxy-5-(2-methoxyethoxy)-N-methylbenzamide (O3.043; 1.35 g) was dissolved in THF (40 ml), methylmagnesium bromide (3.05 ml, 3 M in ether) was added dropwise at 0°C and then the mixture was stirred at RT for 2 h. Then the mixture was admixed with 1 N hydrochloric acid (50 ml), diluted with water and extracted by shaking three times with EA. Then the combined EA phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel (40 g cartridge, n-heptane/EA gradient of 0-30% in 30 min). 1.0 g of the title compound were obtained.

LC-MS rt: 1.58 min $[M+H]^+$: 251.3 (met. a)

O2.044

1-[3-Morpholin-4-yl-5-(pentafluorosulfanyl)phenyl]ethanone

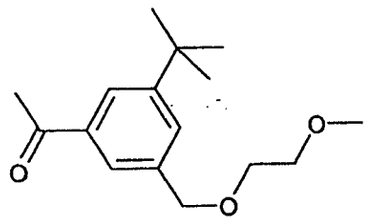


N-Methoxy-N-methyl-3-morpholin-4-yl-5-(pentafluorosulfanyl)benzamide (O3.044; 2.38 g) was converted and worked up analogously to O2.043. The purification was effected using silica gel (80 g cartridge, n-heptane/EA gradient of 0-70% within 40 min). 1.1 g of the title compound were obtained.

LC-MS rt: 1.57 min $[M+H]^+$: 332.0 (met. a)

O2.045

1-[3-tert-Butyl-5-(2-methoxyethoxymethyl)phenyl]ethanone

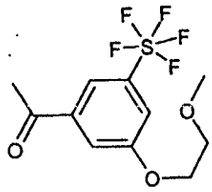


Methyl 3-tert-butyl-5-hydroxymethylbenzoate (6.0 g) was reacted analogously to O5.043 with 1-bromo-2-methoxyethane to give methyl 3-tert-butyl-5-(2-methoxyethoxymethyl)-benzoate. The latter was then converted to the title compound analogously to the sequence O4.043 to O2.043. 508 mg of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.85 (1 H); 7.73 (1 H); 7.63 (1 H); 4.56 (2 H); 3.58 (2 H); 3.50 (2 H); 3.26 (3 H); 2.58 (3 H); 1.32 (9 H)

O2.050

1-[3-(2-Methoxyethoxy)-5-(pentafluorosulfanyl)phenyl]ethanone

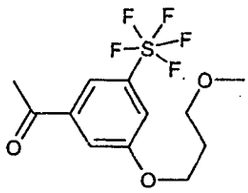


1-[3-Hydroxy-5-(pentafluorosulfanyl)phenyl]ethanone (O3.050; 592 mg) and 1-bromo-2-

methoxyethane (255 µl) were dissolved in DMF (14.8 ml), and sodium hydride (65 mg) was added. After stirring at RT for 2 h, further bromide (80 µl) was added and the mixture was heated to 50°C for 12 h. Then the DMF was drawn off and the residue was taken up in EA, washed with water, dried, filtered and concentrated. 578 mg of the title compound were obtained. LC-MS rt: 1.58 min $[M+H]^+$: 321.1 (met. a)

O2.051

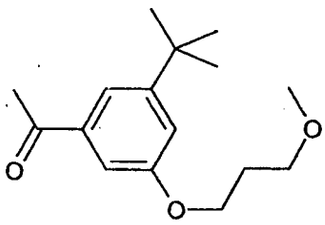
1-[3-(2-Methoxyethoxy)-5-(pentafluorosulfanyl)phenyl]ethanone



1-[3-Hydroxy-5-(pentafluorosulfanyl)phenyl]ethanone (O3.050; 700 mg) and 1-bromo-2-methoxypropane (490 mg) were dissolved in DMF (10 ml), and sodium hydride (77 mg) was added. After stirring at RT for 2 h, further bromide (100 µl) was added and the mixture was heated to 50°C for 6 h. Then the DMF was drawn off and the residue was taken up in EA, washed with water, dried, filtered and concentrated. 670 mg of the title compound were obtained. LC-MS rt: 1.71 min $[M+H]^+$: 335.1 (met. a)

O2.052

1-[3-tert-Butyl-5-(3-methoxypropoxy)phenyl]ethanone

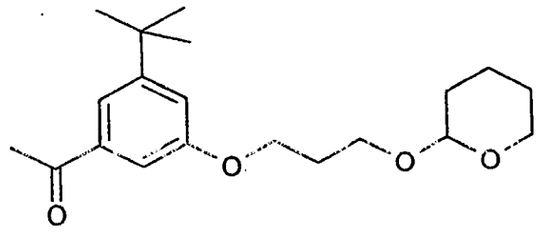


Proceeding from methyl 3-tert-butyl-5-hydroxybenzoate (O6.043) and 1-bromo-3-methoxy-propane, the synthesis sequence O5.043 to O2.043 was followed. 880 mg of the title compound were obtained.

LC-MS-rt: 1.71 min $[M+H]^+$: 265.3 (met. a)

O2.059

1-[3-tert-Butyl-5-(3-hydroxypropoxy)phenyl]ethanone

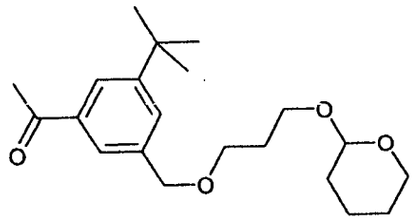


3-tert-Butyl-N-methoxy-N-methyl-5-[3-(tetrahydropyran-2-yloxy)propoxy]benzamide (O3.059; 5.49 g) was dissolved in THF (100 ml), cooled to 0°C and admixed with lithium bis(trimethylsilyl)amide (14.47 ml, 1 M in MTB ether). After stirring at 0°C for 30 min, methylmagnesium bromide (9.65 ml, 3 M in ether) was added dropwise. The cooling bath was removed and, after stirring at RT for 2 h, the mixture was diluted with water and extracted by shaking with EA. The EA phase was dried over magnesium sulfate, filtered and concentrated by rotary evaporation. The residue was purified using silica gel (200 g, n-heptane/EA 4:1). 3.4 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.53 (1 H); 7.28 (1 H); 7.17 (1 H); 4.57 (1 H, -O-C(-C)H-O-); 4.11 (2 H); 2.57 (3 H)

O2.060

1-{3-tert-Butyl-5-[3-(tetrahydropyran-2-yloxy)propoxymethyl]phenyl}ethanone

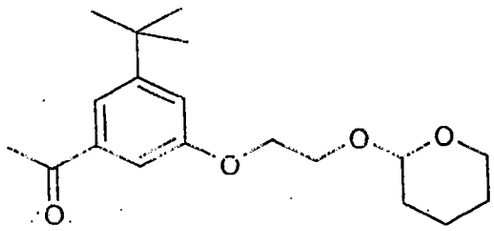


Methyl 3-tert-butyl-5-hydroxymethylbenzoate (3.5 g) was reacted with 2-(3-bromopropoxy)-tetrahydropyran analogously to O5.063 to give methyl 3-tert-butyl-5-[3-(tetrahydropyran-2-yloxy)propoxymethyl]benzoate, and the latter was subsequently converted to the title compound according to the sequence O4.059 to O2.059. 1.75 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.84 (1 H); 7.73 (1 H); 7.61 (1 H); 4.53 (2 H); 4.51 (1 H, -O-C(-C)H-O-), 2.58 (3 H)

O2.061

1-{3-tert-Butyl-5-[2-(tetrahydropyran-2-yloxy)ethoxy]phenyl}ethanone

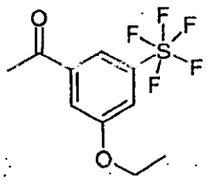


Proceeding from methyl 3-tert-butyl-5-hydroxybenzoate (O6.043) and 2-(2-bromoethoxy)-tetrahydropyran, the synthesis sequence O5.059 to O2.059 was followed. 3.9 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.53 (1 H), 7.31 (1 H), 7.20 (1 H), 4.66 (1 H, -O-C(-C)H-O-), 4.20 (2 H), 2.58 (3 H)

O2.062

1-[3-Ethoxy-5-(pentafluorosulfanyl)phenyl]ethanone

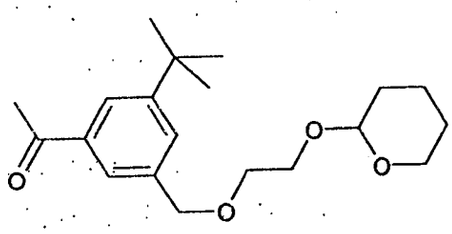


3-Ethoxy-N-methoxy-N-methyl-5-(pentafluorosulfanyl)benzamide (O3.062; 2.60 g) was converted and worked up analogously to O2.007. A purification using silica gel was not carried out. 2.25 g of the title compound were obtained.

LC-MS rt: 1.72 min $[M+H]^+$: 291.0 (met. a)

O2.063

1-{3-tert-Butyl-5-[2-(tetrahydropyran-2-yloxy)ethoxymethyl]phenyl}ethanone



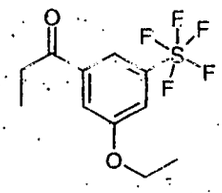
Methyl 3-tert-butyl-5-[2-(tetrahydropyran-2-yloxy)ethoxymethyl]benzoate (O5.063, 2.28 g)

was converted to the title compound analogously to the sequence O4.059 to O2.059. 2.0 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.85 (1 H); 7.74 (1 H); 7.63 (1 H); 4.60 (1 H, -O-C(-C)H-O-), 4.58 (2 H), 2.58 (3 H)

O2.064

1-[3-Ethoxy-5-(pentafluorosulfanyl)phenyl]propan-1-one

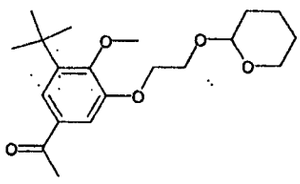


3-Ethoxy-N-methoxy-N-methyl-5-(pentafluorosulfanyl)benzamide (O3.062; 170 mg) was dissolved in absolute THF (5 ml), and ethylmagnesium bromide (0.65 ml; 2 M in diethyl ether) was added dropwise at 0°C while stirring. After addition, the ice bath was removed and the mixture was stirred at RT for 2 h. Then further ethylmagnesium bromide (0.1 ml) was added and the mixture was stirred once again for 2 h. While cooling, 1 N hydrochloric acid was subsequently added dropwise, followed by water and ethyl acetate. The organic phase was removed and the aqueous phase was extracted twice more with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated. 150 mg of the desired compound were obtained.

LC-MS rt: 1.26 min $[M+H]^+$: 305.1 (met. b)

O2.070

1-{3-tert-Butyl-4-methoxy-5-[2-(tetrahydropyran-2-yloxy)ethoxy]phenyl}ethanone

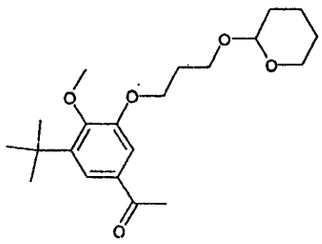


Analogously to O2.071, 1-(3-tert-butyl-5-hydroxy-4-methoxyphenyl)ethanone (O3.070; 5.0 g) was reacted with 2-(2-bromoethoxy)tetrahydropyran (5.64 g). However, the crude product was purified using silica gel (40 g cartridge, n-heptane/EA gradient of 0-50% within 60 min). 6.68 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.50 (2 H, aromatic), 4.70 (1 H, -O-C(-C)H-O-), 3.90 (3 H, -OCH_3), 2.54 (3 H, acetyl)

O2.071

1-{3-tert-Butyl-4-methoxy-5-[3-(tetrahydropyran-2-yloxy)propoxy]phenyl}ethanone

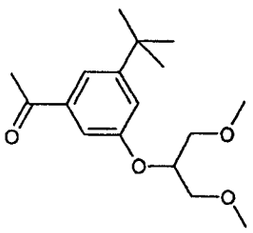


1-(3-tert-Butyl-5-hydroxy-4-methoxyphenyl)ethanone (O3.070; 6.9 g) and 2-(3-bromopropoxy)tetrahydropyran (8.31 g) were dissolved in DMF (80 ml), and sodium hydride (894 mg) was added. After stirring at RT for 5 hours, the solvent was drawn off and the residue was taken up with EA. The EA phase was washed with water, dried and concentrated. 12.7 g of the title compound were obtained as a crude product in sufficient purity.

^{1}H NMR (400 MHz, DMSO-d6) [ppm] (representative signals): 4.57 (1 H, -O-C(-C)H-O-), 2.54 (3 H, acetyl)

O2.072

1-[3-tert-Butyl-5-(2-methoxy-1-methoxymethylethoxy)phenyl]ethanone

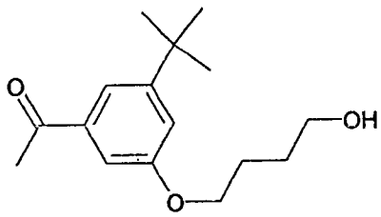


Methyl 3-tert-butyl-5-(2-methoxy-1-methoxymethylethoxy)benzoate (O5.072) was converted to the title compound (1.65 g) analogously to O4.043, O3.059 and O2.043. Chromatography was not carried out at the last stage.

LC-MS rt: 1.63 min $[M+H]^+$: 295.1 (met. a)

O2.073

1-[3-tert-Butyl-5-(4-hydroxybutoxy)phenyl]ethanone

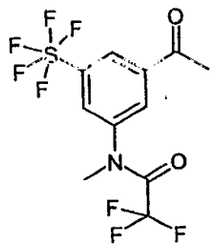


3-tert-Butyl-5-(4-hydroxybutoxy)-N-methoxy-N-methylbenzamide (O3.073; 3.47 g) was converted, worked up and purified analogously to O2.043. The purification using silica gel was carried out as follows: 40 g cartridge, n-heptane/EA gradient of 0-100% within 60 min. 2.08 g of the title compound were obtained.

LC-MS rt: 0.92 min $[M+H]^+$: 265.1 (met. b)

O2.075

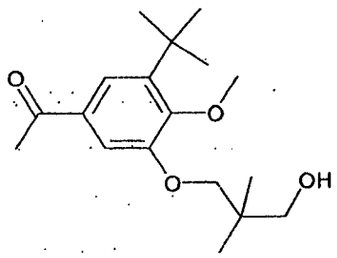
N-[3-Acetyl-5-(pentafluorosulfanyl)phenyl]-2,2,2-trifluoro-N-methylacetamide



In a microwave insert, N-(3-acetyl-5-pentafluorosulfanylphenyl)-2,2,2-trifluoroacetamide (O3.075; 0.25 g) was dissolved in absolute dimethoxyethane (7.5 ml), powdered potassium carbonate was added and the mixture was admixed with iodomethane (80 µl). Subsequently, the mixture was heated in the microwave to 100°C for 40 min. Once further N-(3-acetyl-5-pentafluorosulfanylphenyl)-2,2,2-trifluoroacetamide (4 x 250 mg) had been converted in the manner described, the five batches were worked up together, by decanting from potassium carbonate into 1 N hydrochloric acid with ice cooling. After repeatedly washing the potassium carbonate residue with dimethoxyethane, the aqueous phase was extracted five times with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated. The residue was purified by means of preparative HPLC (met. A). The product-containing fractions were combined, freed of the acetonitrile and extracted five times with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated. 1.03 g of the desired compound were obtained. LC-MS rt: 1.62 min $[M+H]^+$: 372.0 (met. a)

O2.085

1-[3-tert-Butyl-5-(3-hydroxy-2,2-dimethylpropoxy)-4-methoxyphenyl]ethanone

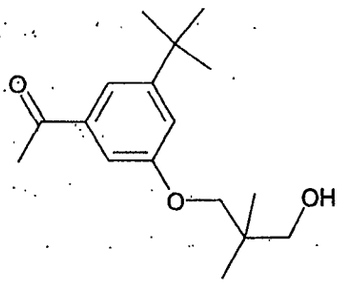


1-(3-tert-Butyl-5-hydroxy-4-methoxyphenyl)ethanone (O3.070; 2.00 g) and 3-bromo-2,2-dimethylpropyl acetate (2.54 g) were dissolved in DMF (15 ml), and cesium carbonate (3.69 g) was added. After stirring at 150°C and max. 15 bar in a microwave for 2.5 h, a further 0.5 eq. of the bromide was added and the mixture was placed into the microwave at 150°C for a further 2 h. Then the mixture was concentrated by rotary evaporation and the residue was partitioned between DCM and water. The DCM phase was removed, dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel (120 g cartridge, n-heptane/MtB ether gradient of 0-50% within 60 min). 1.17 g of the title compound were obtained.

LC-MS rt: 1.92 min $[M+H]^+$: 351.1 (met. a)

O2.086

1-[3-tert-Butyl-5-(3-hydroxy-2,2-dimethylpropoxy)phenyl]ethanone

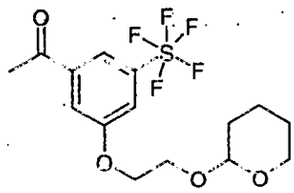


3-tert-Butyl-5-(3-hydroxy-2,2-dimethylpropoxy)-N-methoxy-N-methylbenzamide (O3.086; 910 mg) was converted, worked up and purified analogously to O2.059. 388 mg of the title compound were obtained.

LC-MS rt: 1.65 min $[M+H]^+$: 279.1 (met. a)

O2.090

1-{3-(Pentafluorosulfanyl)-5-[2-(tetrahydropyran-2-yloxy)ethoxy]phenyl}ethanone

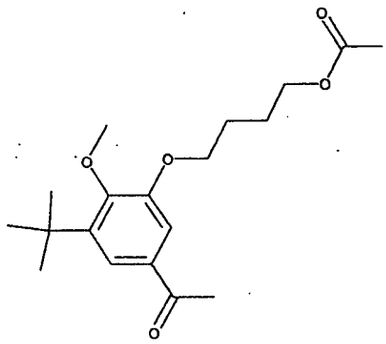


1-[3-Hydroxy-5-(pentafluorosulfanyl)phenyl]ethanone (O3.050; 700 mg) and 2-(2-bromo-ethoxy)tetrahydropyran (670 mg) were dissolved in DMF (15 ml), and sodium hydride (77 mg) was added. After stirring at RT for 2 h, the mixture was heated to 50°C for 4 h and left to stand over the weekend. Then the DMF was drawn off and the residue was taken up in EA. The EA phase was washed with water, dried, filtered and concentrated. The crude product was purified using silica gel (100 g, n-heptane/EA 4:1). 813 mg of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.87 (1 H), 7.80 (1 H), 7.71 (1 H), 4.66 (1 H, -O-C(-C)H-O-), 4.35 (2 H), 2.66 (3 H)

O2.095

4-(5-Acetyl-3-tert-butyl-2-methoxyphenoxy)butyl acetate



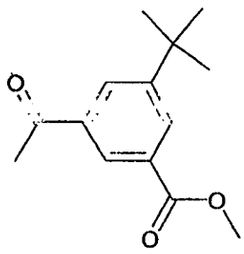
1-(3-tert-Butyl-5-hydroxy-4-methoxyphenyl)ethanone (O3.070; 6.9 g) was converted and worked up analogously to O2.071. The bromide used was 4-bromobutyl acetate (7.27 g). 10.5 g of the title compound were obtained.

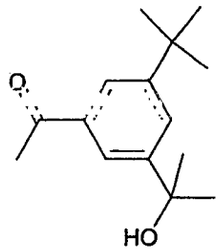
LC-MS rt: 1.14 min $[M+H]^+$: 337.1 (met. b)

O2.100

Methyl 3-acetyl-5-tert-butylbenzoate and 1-[3-tert-butyl-5-(1-hydroxy-1-methylethyl)-

phenyl]ethanone





Methyl 5-tert-butyl-N-methoxy-N-methylisophthalamidate (O3.100; 10.4 g) was dissolved at RT in THF (150 ml) under argon. Thereafter, methylmagnesium bromide (19 ml; 3 M in diethyl ether) was added dropwise at 0°C while stirring. After 10 min, the ice bath was removed and the mixture was stirred at RT for 3.5 h. Then the mixture was admixed with 1 N hydrochloric acid and water while cooling with ice. The aqueous phase was extracted three times with EA and the combined EA phases were dried over sodium sulfate, filtered and concentrated. The residue was purified using silica gel. 7.0 g of methyl 3-acetyl-5-tert-butyl-benzoate and 550 mg of 1-[3-tert-butyl-5-(1-hydroxy-1-methylethyl)phenyl]ethanone were obtained.

Methyl 3-acetyl-5-tert-butylbenzoate

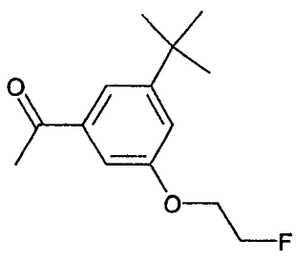
LC-MS rt: 1.13 min $[M+H]^+$: 235.2 (met. b)

1-[3-tert-Butyl-5-(1-hydroxy-1-methylethyl)phenyl]ethanone

LC-MS rt: 1.03 min $[M+H]^+$-OH: 217.2 (met. b)

O2.105

1-[3-tert-Butyl-5-(2-fluoroethoxy)phenyl]ethanone ZSI2.060

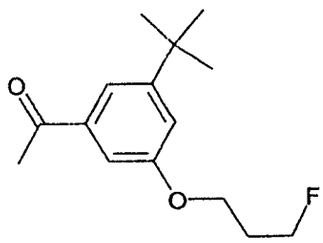


1-(3-tert-Butyl-5-hydroxyphenyl)ethanone (O3.106; 500 mg) was dissolved in DMF (10 ml), and 1-bromo-2-fluoroethane (195 µl) was added while stirring. Sodium hydride (80 mg) was added at RT. After stirring at RT for 3 h, the mixture was left to stand overnight and then

further sodium hydride (20 mg) was added and the mixture was stirred for a further 2 h. Then water was added and the mixture was concentrated to dryness. The residue was taken up in EA and washed three times with water. The EA phase was dried over magnesium sulfate, filtered and concentrated. 600 mg of the title compound were obtained. LC-MS rt: 1.13 min $[M+H]^+$: 239.1 (met. b)

O2.106

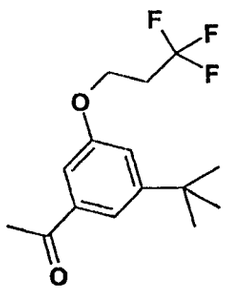
1-[3-tert-Butyl-5-(3-fluoropropoxy)phenyl]ethanone



1-(3-tert-Butyl-5-hydroxyphenyl)ethanone (O3.106; 500 mg) was reacted with 1-bromo-3-fluoropropane (239 µl) and worked up analogously to O2.105. 630 mg of the title compound were obtained. LC-MS rt: 1.16 min $[M+H]^+$: 253.2 (met. b)

O2.107

1-[3-tert-Butyl-5-(3,3,3-trifluoropropoxy)phenyl]ethanone

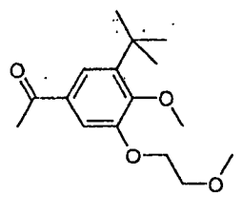


To a solution of 1-(3-tert-butyl-5-hydroxyphenyl)ethanone (O3.106; 300 mg, 1.56 mmol), 3,3,3-trifluoropropanol (178 mg, 1.56 mmol) and triphenylphosphine (409 mg, 1.56 mmol) in dichloromethane (5 ml) at RT was added a solution of di(4-chlorobenzyl) azodicarboxylate (573 mg, 1.56 mmol) in dichloromethane (1 ml). The mixture was stirred for 5 days and then filtered. The solvent was removed and the residue was purified by flash chromatography (n-heptane:ethyl acetate). Yield: 170 mg, 38%.

LC-MS rt: 1.14 min $[M+H]^+$: 289.2 (met. b)

O2.110

1-[3-tert-Butyl-4-methoxy-5-(2-methoxyethoxy)phenyl]ethanone

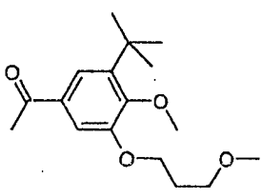


1-(3-tert-Butyl-5-hydroxy-4-methoxyphenyl)ethanone (O3.070; 2.00 g) and 1-bromo-2-methoxyethane (1.5 g) were dissolved in DMF (20 ml), and sodium hydride (259 mg) was added. After stirring at RT for 3 h, the mixture was left to stand overnight. Then the DMF was drawn off and the residue was taken up in EA. The EA phase was washed with water, dried, filtered and concentrated. The residue was purified using silica gel (80 g cartridge, n-heptane/EA 0-40% within 60 min). 1.17 g of the title compound were obtained.

LC-MS rt: 1.03 min $[M+H]^+$: 281.1 (met. b)

O2.111

1-[3-tert-Butyl-4-methoxy-5-(3-methoxypropoxy)phenyl]ethanone



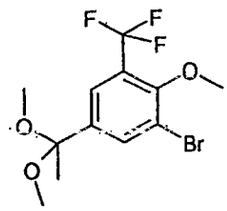
1-(3-tert-Butyl-5-hydroxy-4-methoxyphenyl)ethanone (O3.070; 2.00 g) and 1-bromo-3-methoxypropane (1.65 g) were converted, worked up and purified analogously to O2.110. 1.50 g of the title compound were obtained.

LC-MS rt: 1.09 min $[M+H]^+$: 295.2 (met. b)

O3

O3.004

1-Bromo-5-(1,1-dimethoxyethyl)-2-methoxy-3-trifluoromethylbenzene

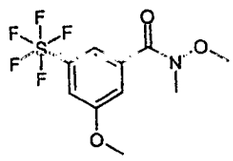


1-(3-Bromo-4-hydroxy-5-trifluoromethylphenyl)ethanone (O4.004; 6.8 g) was dissolved in methanol (50 ml) and admixed successively with DL-10-camphorsulfonic acid (111 mg) and trimethyl orthoformate (8 ml). After stirring at RT for 2 h, DMF (75 ml), potassium carbonate (4.98 g) and then slowly, while cooling with ice, iodomethane (3 ml) were added. After stirring at RT for 4 h, the reaction mixture was left to stand overnight and then admixed with n-heptane/water, and the organic phase was removed. The aqueous phase was extracted by shaking once more with n-heptane, and the combined organic phases were then dried over magnesium sulfate, filtered and concentrated. 7 g of the title compound were obtained in sufficient purity.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.90 (1 H), 7.62 (1 H), 3.89 (3 H), 3.10 (6 H), 1.49 (3 H)

O3.007

3,N-Dimethoxy-N-methyl-5-(pentafluorosulfanyl)benzamide



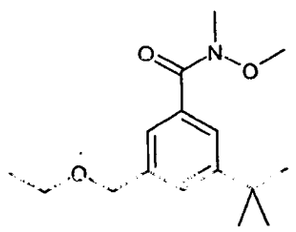
Methyl 3-methoxy-5-(pentafluorosulfanyl)benzoate (O4.007; 2.5 g) was dissolved in absolute THF (65 ml), and N,O-dimethylhydroxylamine hydrochloride (1.2 g) was added. Then the mixture was cooled to -15°C and isopropylmagnesium bromide solution (13.59 ml, 2 M in THF) was added dropwise. After 20 min, the cooling bath was removed and the mixture was stirred at RT for 1 h. Then ammonium chloride solution was added and the aqueous phase was extracted three times with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated. The crude product thus obtained still contained significant reactant, and was therefore converted and worked up again as described above. No reactant was present any longer in the residue which was then obtained. Purification was effected by means of preparative HPLC (met. A). The product-containing fractions were

combined and freed of the acetonitrile, and the aqueous phase was extracted three times with EA. The combined extracts were dried over magnesium sulfate, filtered and concentrated. 1.78 g of the desired compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$) [ppm]: 7.70 (1 H), 7.37 (1 H), 7.24 (1 H + $CDCl_3$), 3.88 (3 H), 3.56 (3 H)

O3.008

3-tert-Butyl-5-ethoxymethyl-N-methoxy-N-methylbenzamide

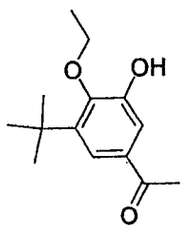


Analogously to O3.043, 3-tert-butyl-5-ethoxymethylbenzoic acid (O4.008; 1.15 g) was first converted to the acid chloride (1.24 g), and then the 3-tert-butyl-5-ethoxymethylbenzoyl chloride obtained was converted further. 854 mg of the title compound were obtained.

LC-MS rt: 3.32 min $[M+H]^+$: 280.2 (met. d)

O3.010

1-(3-tert-Butyl-4-ethoxy-5-hydroxyphenyl)ethanone

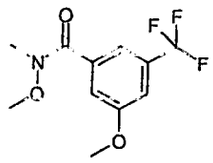


1-Bromo-3-tert-butyl-5-(1,1-dimethoxyethyl)-2-ethoxybenzene (O4.010; 19.68 g) was converted analogously to O3.070. 5.15 g of the title compound were obtained.

LC-MS rt: 0.972 min $[M+H]^+$: 237.1 (met. b)

O3.014

3,N-Dimethoxy-N-methyl-5-trifluoromethylbenzamide

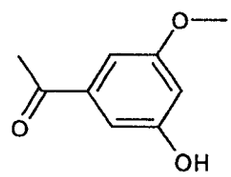


Methyl 3-methoxy-5-trifluoromethylbenzoate (O4.014, 1 g) and N,O-dimethylhydroxylamine (416 mg) were initially charged in THF (30 ml). Thereafter, the mixture was cooled to -15°C, and isopropylmagnesium chloride (3.2 ml; 2 M in THF) was added dropwise within 10 min. The mixture was stirred at -15°C for another 20 min before the cooling bath was removed. After 3 h, the mixture was cooled again to -15°C and further isopropylmagnesium chloride (3.2 ml) was added. After the cooling bath had been removed, the mixture was stirred at RT for another hour, then admixed with 20% ammonium chloride solution and extracted three times with EA. The combined EA phases were dried over sodium sulfate, filtered and concentrated. The residue was purified using silica gel (50 g cartridge, DCM as eluent). 465 mg of the title compound were obtained, as well as 427 mg of reactant.

LC-MS rt: 1.36 min $[M+H]^+$: 264.0 (met. a)

O3.033

1-(3-Hydroxy-5-methoxyphenyl)ethanone

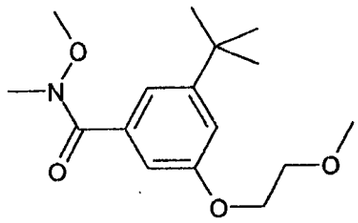


1-(3,5-Dihydroxyphenyl)ethanone (3 g) and methyl iodide (2.80 g) were dissolved in DMF (40 ml), and sodium hydride (568 mg) was added. After stirring at RT for 2 h, the DMF was drawn off. The residue was taken up in EA and washed with water, dried, filtered and concentrated. The residue was purified using silica gel (89 g cartridge, n-heptane/EA 0-50% within 30 min). 1.12 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 9.8 (1 H); 6.93 (2 H); 6.58 (1 H); 3.76 (3 H); 2.50 (3 H + DMSO)

O3.043

3-tert-Butyl-N-methoxy-5-(2-methoxyethoxy)-N-methylbenzamide

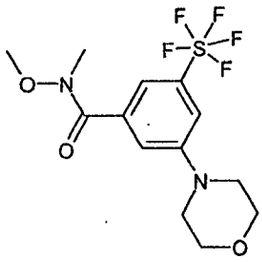


3-tert-Butyl-5-(2-methoxyethoxy)benzoic acid (O4.043; 1.9 g) was dissolved in thionyl chloride (10.9 ml), kept under reflux for 2 h and then concentrated. The resulting 3-tert-butyl-5-(2-methoxyethoxy)benzoyl chloride (2.04 g) was dissolved in DCM (20 ml) and admixed with dimethylhydroxylamine (734 mg), then Hünig's base (1.37 ml) was added and the mixture was stirred at RT for 1 h. Then the mixture was dried, the residue was taken up in EA, and the mixture was washed four times with water, dried over magnesium sulfate, filtered and concentrated by rotary evaporation. The residue was purified using silica gel (40 g cartridge, n-heptane/EA gradient of 0-50% in 40 min). 1.36 g of the title compound were obtained.

LC-MS rt: 1.43 min $[M+H]^+$: 296.3 (met. a)

O3.044

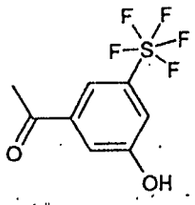
N-Methoxy-N-methyl-3-morpholin-4-yl-5-(pentafluorosulfanyl)benzamide



3-Amino-N-methoxy-N-methyl-5-(pentafluorosulfanyl)benzamide (O5.075; 6.3 g) was dissolved in DMF (80 ml), and cesium carbonate (10.1 g), sodium iodide (0.62 g) and bis(2-bromoethyl) ether (19.37 g) were added. The mixture was divided between 10 microwave vessels, each of which was heated to 130°C for 3 h. Subsequently, the batches were combined and freed of solvent. The residue was taken up in EA and washed with water. The EA phase was dried and concentrated. The residue was purified using silica gel (120 g cartridge, n-heptane/EA gradient of 0-100% within 30 min). 2.48 g of the title compound were obtained. LC-MS rt: 1.41 min $[M+H]^+$: 377.0 (met. a)

O3.050

1-[3-Hydroxy-5-(pentafluorosulfanyl)phenyl]ethanone

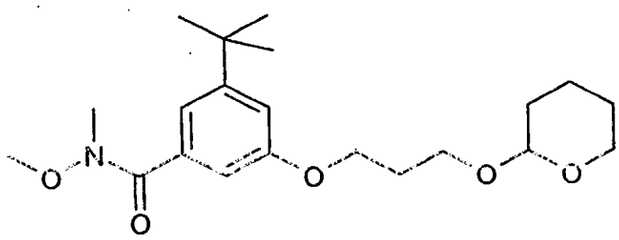


1-[3-Amino-5-(pentafluorosulfanyl)phenyl]ethanone (O4.050; 3.00 g) was dissolved in 35% aqueous sulfuric acid (25 ml) while heating. The solution was cooled to -5°C and a solution of sodium nitrite (780 mg) in 15 ml of water was added dropwise within 10 min. After 40 min at -5°C, the cooling bath was removed and the mixture was heated to 100°C for 2 h. After cooling, the mixture was extracted twice with EA. The combined EA phases were washed with saturated sodium hydrogencarbonate solution, dried, filtered and concentrated. The residue was purified using silica gel (80 g cartridge, n-heptane/MtB ether gradient of 0-100% within 40 min). 1.62 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 10.71 (1 H), 7.73 (1 H), 7.59 (1 H), 7.47 (1 H), 2.61 (3 H)

O3.059

3-tert-Butyl-N-methoxy-N-methyl-5-[3-(tetrahydropyran-2-yloxy)propoxy]benzamide

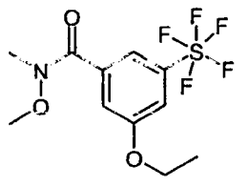


3-tert-Butyl-5-[3-(tetrahydropyran-2-yloxy)propoxy]benzoic acid (O4.059; 4.90 g) and N,O-dimethylhydroxylamine hydrochloride (1.42 g) were dissolved in DMF (80 ml) and admixed with Hünig's base (4.81 ml) and TOTU (4.78 g). After stirring for 2 h, the mixture was left to stand overnight. Then the DMF was drawn off, the mixture was partitioned between EA and saturated sodium hydrogencarbonate solution, and the EA phase was removed, dried over magnesium sulfate, filtered and concentrated. 5.49 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.12 (1 H), 7.01 (1 H), 6.90 (1 H), 4.56 (1 H, -O-C(-C)H-O-), 4.06 (2 H), 3.57 (3 H), 3.22 (3 H)

O3.062

3-Ethoxy-N-methoxy-N-methyl-5-(pentafluorosulfanyl)benzamide

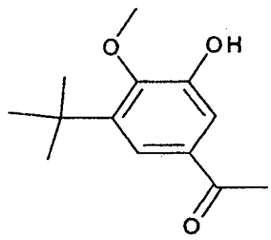


Ethyl 3-ethoxy-5-(pentafluorosulfanyl)benzoate (O4.062; 4.80 g) was converted and worked up analogously to O3.007. The residue was purified using silica gel (120 g cartridge, n-heptane/MtB ether gradient 20-100% within 60 min). 2.80 g of the title compound were obtained.

LC-MS rt: 1.60 min $[M+H]^+$: 336.0 (met. a)

O3.070

1-(3-tert-Butyl-5-hydroxy-4-methoxyphenyl)ethanone

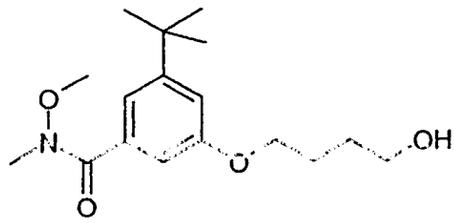


1-Bromo-3-tert-butyl-5-(1,1-dimethoxyethyl)-2-methoxybenzene (O4.070; 36.3 g) was dissolved in THF (1 l), n-butyllithium (52.6 ml; 2.5 M in hexane) was added dropwise at -75°C under argon, and the mixture was stirred for a further 30 min. Then trimethyl borate (37.3 ml) was added dropwise and the mixture was allowed to come to RT within 2 h. Subsequently, sodium hydroxide (4.4 g, dissolved in 10 ml of water) and hydrogen peroxide solution (62.3 ml; 35% in water) were added successively. After stirring at RT for 2 h, the mixture was left to stand overnight. Then water and EA were added and the mixture was acidified with hydrochloric acid. After removing the EA phase, this was dried over magnesium sulfate and concentrated. The residue was purified using silica gel (330 g cartridge, n-heptane/EA gradient of 0-50% within 60 min). 14 g of the title compound were obtained.

LC-MS rt: 0.90 min $[M+H]^+$: 223.1 (met. b)

O3.073

3-tert-Butyl-5-(4-hydroxybutoxy)-N-methoxy-N-methylbenzamide

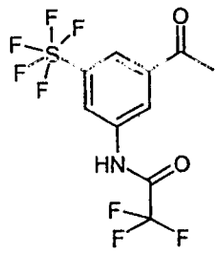


3-tert-Butyl-5-(4-hydroxybutoxy)benzoic acid (O4.073; 4.13 g) was converted and worked up analogously to O3.059. For further purification, chromatography was effected using silica gel as follows: 80 g cartridge, n-heptane/EA gradient of 0-100% within 60 min. 3.47 g of the title compound were obtained.

LC-MS rt: 0.86 min $[M+H]^+$: 310.3 (met. b)

O3.075

N-(3-Acetyl-5-pentafluorosulfanylphenyl)-2,2,2-trifluoroacetamide



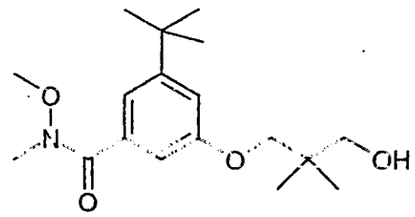
N-Methoxy-N-methyl-3-(pentafluorosulfanyl)-5-(2,2,2-trifluoroacetylamino)benzamide (O4.075; 1.65 g) was dissolved in THF (25 ml). At 0°C, lithium bis(trimethylsilyl)amide (0.9 ml) was added while stirring. After 30 min, methylmagnesium bromide (3.5 ml, 3 M in diethyl ether) was added dropwise. After the addition had ended, the ice bath was removed and the mixture was stirred at RT for 2 h. While cooling, 1 N hydrochloric acid, water and EA were then added. After removing the organic phase, the aqueous phase was extracted twice more with EA. The combined EA phases were dried with magnesium sulfate, filtered and concentrated. The crude product is a mixture of N-(3-acetyl-5-pentafluorosulfanyl-phenyl)-2,2,2-trifluoroacetamide and 1-[3-amino-5-(pentafluorosulfanyl)phenyl]ethanone, and so the crude product (1.3 g) was taken up in methylene chloride (60 ml) and admixed with triethylamine (155 µl). Thereafter, trifluoroacetic anhydride (160 µl) was added while stirring. After stirring at RT for 3 h, water and saturated sodium hydrogencarbonate solution

were added, the phases were separated and the DCM phase was washed three times more with water. The DCM phase was dried with magnesium sulfate, filtered and concentrated. 1.3 g of the title compound were obtained.

LC-MS rt: 1.61 min $[M+H]^+$: 358.0 (met. a)

O3.086

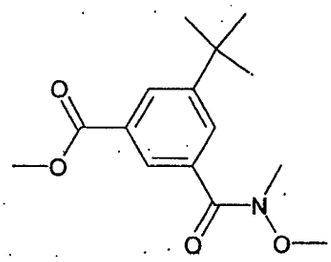
3-tert-Butyl-5-(3-hydroxy-2,2-dimethylpropoxy)-N-methoxy-N-methylbenzamide



3-tert-Butyl-5-(3-hydroxy-2,2-dimethylpropoxy)benzoic acid (O4.086; 940 mg) was converted and worked up analogously to O3.059. 910 mg of the title compound were obtained. LC-MS rt: 1.50 min $[M+H]^+$: 324.1 (met. a)

O3.100

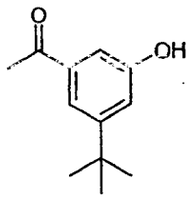
Methyl 5-tert-butyl-N-methoxy-N-methylisophthalamidate



Monomethyl 5-tert-butylisophthalate (10.0 g) was converted, worked up and purified analogously to O3.043. 10.6 g of the title compound were obtained. LC-MS rt: 1.06 min $[M+H]^+$: 280.2 (met. b)

O3.106

1-(3-*tert*-Butyl-5-hydroxyphenyl)ethanone



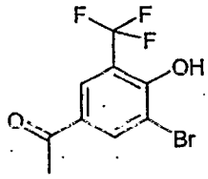
m-Chloroperbenzoic acid (382 g, 2.21 mol) was added to a solution of 1,3-bisacetyl-5-*tert*-butylbenzene (O4.106; 169 g, 776 mmol) in dichloromethane (1.7 l). The resulting suspension was heated to reflux temperature for 24 h. Once the suspension had cooled, the solids were filtered off and the filtrate was admixed with saturated aqueous $NaHSO_3$ solution (500 ml). The phases were separated, the organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was dissolved in THF (500 ml) and admixed with lithium hydroxide (34.9 g, 1.46 mol). After 4 h at RT, aqueous sodium hydroxide solution (1 M, 500 ml) was added and the mixture was washed with MtB ether (3 × 500 ml). The aqueous phase was acidified (pH 3) with HCl (1 M), and extracted with EA (3 × 500 ml). The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (met. C). The product was obtained as a colorless oil which crystallized slowly (36.5 g).

LC-MS rt: 1.30 min $[M+H]^+$: 193 (met. a)

O4

O4.004

1-(3-Bromo-4-hydroxy-5-trifluoromethylphenyl)ethanone

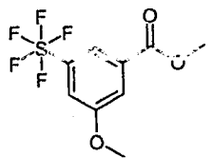


1-(4-Hydroxy-3-trifluoromethylphenyl)ethanone (5 g) was initially charged in acetonitrile (150 ml) at RT while stirring, and cooled to -10°C. At this temperature, N-bromosuccinimide (4.5 g, dissolved in 100 ml of acetonitrile) was added dropwise. Then the cooling bath was removed and the mixture was stirred for a further 5 h. After standing overnight, ¾ of the solvent was drawn off and the residue was admixed with n-heptane/water. The organic phase was removed and washed once with 5% sodium thiosulfate solution and once with water. The

precipitate formed was filtered off with suction, washed and dried. 6.9 g of the title compound were obtained in sufficient purity. LC-MS rt: 1.35 min $[M+H]^+$: 283.0 (met. a)

O4.007

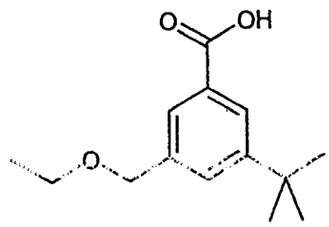
Methyl 3-methoxy-5-(pentafluorosulfanyl)benzoate



3-Hydroxy-5-(pentafluorosulfanyl)benzoic acid (O5.007; 3.0 g) was dissolved in absolute DMF (75 ml). Then iodomethane (3.6 ml) was added while stirring, followed by finely powdered potassium carbonate (6.3 g). After stirring at 40°C for 5 hours, the mixture was cooled and admixed with water (250 ml). The mixture was then extracted four times with ether (100 ml). The combined extracts were each washed once with 1 N sodium hydroxide solution (75 ml) and water (100 ml), dried over magnesium sulfate, filtered and concentrated. 2.9 g of the desired compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$) [ppm]: 8.00 (1 H), 7.70 (1 H), 7.47 (1 H), 3.96 (3 H), 3.90 (3 H)

O4.008



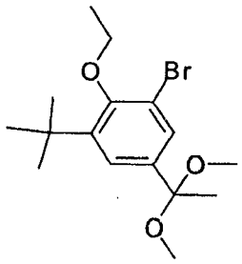
3-tert-Butyl-5-ethoxymethylbenzoic acid

Methyl 3-tert-butyl-5-ethoxymethylbenzoate (O5.008; 1.18 g) was converted analogously to O4.043. However, the crude product obtained was subsequently purified using silica gel (50 g cartridge, n-heptane/EA gradient of 0-50% within 30 min). 1.15 g of the title compound were obtained.

^{1}H NMR (400 MHz, DMSO-d_6) [ppm]: 12.90 (1 H), 7.86 (1 H), 7.73 (1 H), 7.57 (1 H), 4.50 (2 H), 3.50 (1 H), 1.30 (9 H), 1.16 (3 H)

O4.010

1-Bromo-3-tert-butyl-5-(1,1-dimethoxyethyl)-2-ethoxybenzene

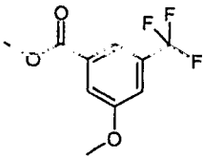


2-Bromo-6-tert-butyl-4-(1,1-dimethoxyethyl)phenol (20 g; for synthesis see CA02515715) was alkylated with ethyl iodide analogously to the conditions of O4.070. 19.67 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.46 (1 H), 7.33 (1 H), 4.03 (2 H), 3.06 (6 H), 1.43 (3 H), 1.38 (3 H), 1.35 (9 H)

O4.014

Methyl 3-methoxy-5-trifluoromethylbenzoate

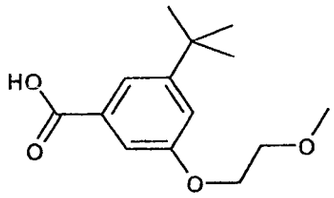


3-Hydroxy-5-trifluoromethylbenzoic acid (2 g) was initially charged at RT in DMF (15 ml) while stirring, and admixed dropwise with methyl iodide (3.0 ml). After adding potassium carbonate (5.6 g), the mixture was stirred for 5 h and left to stand overnight. It was then admixed with water and extracted three times with MtB ether. The combined MTB ether phases were dried over sodium sulfate, filtered and concentrated. 2.29 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.76 (1 H), 7.70 (1 H), 7.55 (1 H), 3.91 (3 H), 3.89 (3 H)

O4.043

3-tert-Butyl-5-(2-methoxyethoxy)benzoic acid

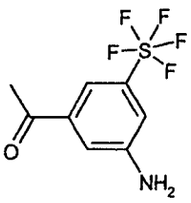


Methyl 3-tert-butyl-5-(2-methoxyethoxy)benzoate (O5.043; 2.0 g) was dissolved in methanol (30 ml) and THF (60 ml), and lithium hydroxide solution (30 ml, 1 M in water) was added. The mixture was heated to 40°C and stirred for 3 h. Then the organic solvents were drawn off and the aqueous phase was adjusted to pH 3 with 1 N hydrochloric acid. The mixture was extracted with EA, dried, filtered and concentrated. 1.9 g of the title compound were obtained.

LC-MS rt: 1.40 min $[M+H-H_2O]^+$: 235.3 (met. a)

O4.050

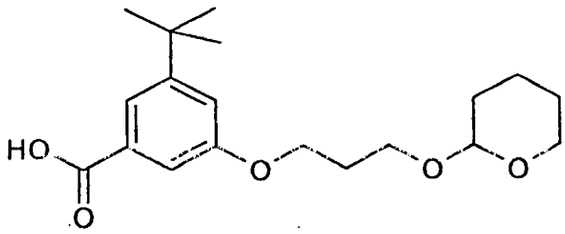
1-[3-Amino-5-(pentafluorosulfanyl)phenyl]ethanone



N-(3-Acetyl-5-pentafluorosulfanylphenyl)-2,2,2-trifluoroacetamide (O3.075; 9.4 g) was admixed with semiconcentrated sulfuric acid (200 ml), and DCM (15 ml) was added. After stirring at 100°C for 7 h, the mixture was left to stand overnight. Then the mixture was added to ice-water and extracted with EA. The combined EA phases were washed with saturated sodium hydrogencarbonate solution, dried over magnesium sulfate, filtered and concentrated by rotary evaporation. 6.36 g of the title compound were obtained. LC-MS rt: 1.38 min $[M+H]^+$: 262.0 (met. a)

O4.059

3-tert-Butyl-5-[3-(tetrahydropyran-2-yloxy)propoxy]benzoic acid

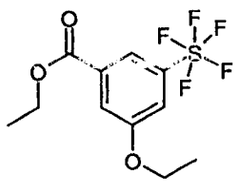


Methyl 3-tert-butyl-5-[3-(tetrahydropyran-2-yloxy)propoxy]benzoate (O5.059; 5.37 g) was dissolved in methanol (80 ml) and THF (160 ml), and lithium hydroxide solution (61.28 ml, 1 M in water) was added. After stirring at 40°C for 2 h, the mixture was dried, and the residue was taken up with water and freeze-dried. The product obtained was stirred with DCM, filtered and dried. 4.9 g of product were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.52 (1 H), 7.26 (1 H), 6.80 (1 H), 4.57 (1 H, -O-C(-C)H-O-), 4.02 (2 H)

O4.062

Ethyl 3-ethoxy-5-(pentafluorosulfanyl)benzoate

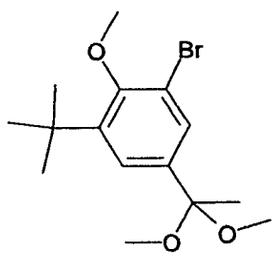


3-Hydroxy-5-(pentafluorosulfanyl)benzoic acid (O5.007; 4.76 g) was reacted with ethyl iodide (7.27 ml) and worked up analogously to O4.007. 4.80 g of the title compound were obtained.

LC-MS rt: 1.97 min $[M+H]^+$: 321.0 (met. a)

O4.070

1-Bromo-3-tert-butyl-5-(1,1-dimethoxyethyl)-2-methoxybenzene



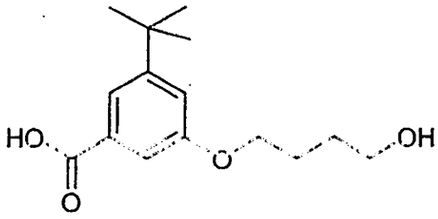
1-Bromo-3-tert-butyl-5-(1,1-dimethoxyethyl)-2-methoxybenzene was synthesized

analogously to patent application CA 02515715.

^{1}H NMR (500 MHz, DMSO-d6) [ppm]: 7.47 (1 H), 7.33 (1 H), 3.85 (3 H), 3.07 (6 H), 1.43 (3 H), 1.35 (9 H)

O4.073

3-tert-Butyl-5-(4-hydroxybutoxy)benzoic acid

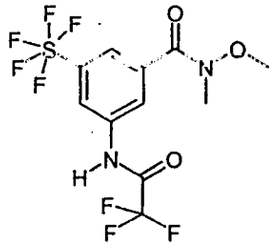


Methyl 3-tert-butyl-5-hydroxybenzoate (O6.043; 3.3 g) was reacted with 4-bromobutyl acetate (3.71 g) and worked up analogously to O5.043. The crude product was hydrolyzed directly, analogously to O4.086, with lithium hydroxide to give the title compound (4.13 g).

LC-MS rt: 0.84 min $[M+H]^+$: 267.1 (met. b)

O4.075

N-Methoxy-N-methyl-3-(pentafluorosulfanyl)-5-(2,2,2-trifluoroacetylamino)benzamide

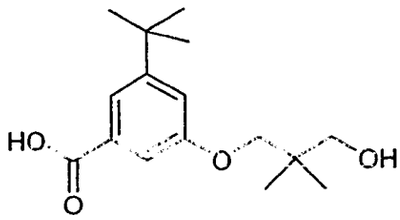


3-Amino-N-methoxy-N-methyl-5-pentafluorosulfanylbenzamide (O5.075; 1.45 g) was dissolved in methylene chloride (15 ml), and, while stirring, triethylamine (0.8 ml) followed by trifluoroacetic anhydride (0.85 ml) were added with exclusion of moisture. After stirring at RT for 3 h and standing overnight, water and saturated sodium hydrogencarbonate solution were added, the phases were separated and the methylene chloride phase was washed three times more with water, dried over magnesium sulfate, filtered and concentrated. The product obtained (1.75 g) was used in the next stage without further purification.

LC-MS rt: 1.53 min $[M+H]^+$: 403.0 (met. a)

O4.086

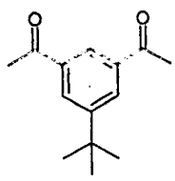
3-tert-Butyl-5-(3-hydroxy-2,2-dimethylpropoxy)benzoic acid



Methyl 3-(3-acetoxy-2,2-dimethylpropoxy)-5-tert-butylbenzoate (O5.086; 1 g) was dissolved in methanol/THF (15/30 ml), and lithium hydroxide solution (11.89 ml, 1 M in water) was added. After stirring at 40°C for 2 h, the organic solvent was drawn off, and the residue was diluted with water and adjusted to pH 3 with 1 N hydrochloric acid. Then it was extracted with EA, and the combined organic phases were dried, filtered and concentrated. 940 mg of the title compound were obtained. LC-MS rt: 1.45 min $[M+H]^+$: 281.1 (met. a)

O4.106

1,3-Bisacetyl-5-*tert*-butylbenzene

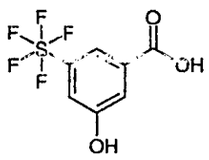


In a 4 l three-neck flask with a mechanical stirrer, a solution of 5-tert-butyl-N,N'-dimethoxy-N,N'-dimethylisophthalamide (O5.106; 254 g, 560 mmol) in THF (700 ml) was slowly added dropwise within 2 h to methylmagnesium bromide (3 M in Et_2O, 1.49 l, 4.48 mol). The solution was cooled during the addition, such that the temperature was kept between -10°C and +5°C. On completion of addition, the cooling was removed and the reaction solution was stirred at RT for 16 h. The reaction solution was then added slowly to a cooled mixture of HCl (1 M, 500 ml) and ice. During this hydrolysis, the pH was kept between 3 and 6 by the addition of concentrated HCl. On completion of addition, MtB ether (1 l) was added. The phases were separated and the aqueous phase was extracted with MtB ether (1 × 500 ml). The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The product was obtained as a colorless oil (123 g). LC-MS rt: 1.50 min $[M+H]^+$: 219 (met. a)

O5

O5.007

3-Hydroxy-5-(pentafluorosulfanyl)benzoic acid

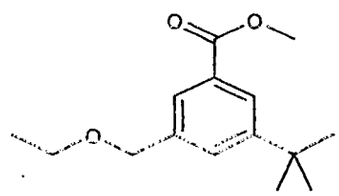


3-Amino-5-pentafluorosulfanylbenzoic acid (O6.007; 3.9 g) was dissolved in 35% sulfuric acid (120 ml) and cooled to -5°C, and a solution of sodium nitrite (1.1 g) in water (100 ml) was added dropwise within 10 min. After 40 min, further nitrite solution was added (2 ml), and another 2 ml and 1 ml after a further 20 min in each case. Then the cooling bath was removed and the mixture was heated to 100°C. After 5 h, the mixture was cooled and the solution was decanted. The clear, acidic solution was extracted five times with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated. The crude product was recrystallized from ethyl acetate/heptane. 3.6 g of the desired compound were obtained.

^{1}H NMR (400 MHz, DMSO-d_6) [ppm]: 10.72 (1 H); 7.71 (1 H); 7.57 (1 H); 7.46 (1 H)

O5.008

Methyl 3-tert-butyl-5-ethoxymethylbenzoate

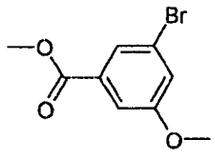


Methyl 3-tert-butyl-5-hydroxymethylbenzoate (2.0 g) was alkylated with ethyl iodide analogously to the conditions of O5.043. 1.18 g of the title compound were obtained.

LC-MS rt: 3.81 min $[M+H]^+$: 250.2 (met. d)

O5.032

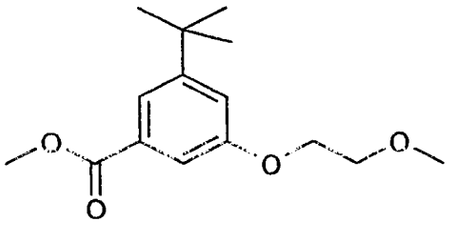
Methyl 3-bromo-5-methoxybenzoate



Methyl 3-bromo-5-hydroxybenzoate (O6.032; 2.52 g) was alkylated with methyl iodide and worked up analogously to the conditions of O5.043. 2.5 g of the title compound were obtained. LC-MS rt: 1.58 min $[M+H]^+$: 245.0 (met. a)

O5.043

Methyl 3-tert-butyl-5-(2-methoxyethoxy)benzoate

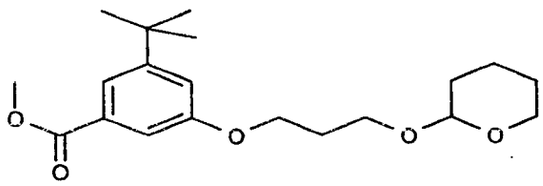


Methyl 3-tert-butyl-5-hydroxybenzoate (O6.043; 2.18 g) and 1-bromo-2-methoxyethane (1.18 ml) were dissolved in DMF (30 ml) and sodium hydride (301 mg) was added while stirring. After stirring at RT for 2 h, the solvent was drawn off. The residue was taken up in EA, and the mixture was washed with water, dried and concentrated. The residue was purified using silica gel (80 g cartridge, n-heptane/MtB ether gradient of 0-30% in 60 min). 2.0 g of the title compound were obtained.

LC-MS rt: 1.69 min $[M+H-HOCH_3]^+$: 235.2 (met. a)

O5.059

Methyl 3-tert-butyl-5-[3-(tetrahydropyran-2-yloxy)propoxy]benzoate



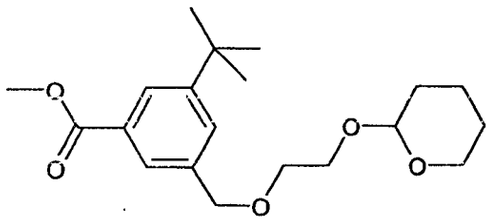
Methyl 3-tert-butyl-5-hydroxybenzoate (O6.043; 3.22 g) and 2-(3-bromopropoxy)-tetrahydropyran (4.14 g) were dissolved in DMF (30 ml), and sodium hydride (445 mg) was added. After stirring at RT for 3 h, the mixture was left to stand overnight. Then the DMF was drawn off and the residue was taken up in EA, washed with water, dried, filtered and

concentrated. 5.37 g of product were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.56 (1 H), 7.28 (1 H), 7.19 (1 H), 4.57 (1 H, -O-C(-C)H-O-), 4.10 (2 H)

O5.063

Methyl 3-tert-butyl-5-[2-(tetrahydropyran-2-yloxy)ethoxymethyl]benzoate

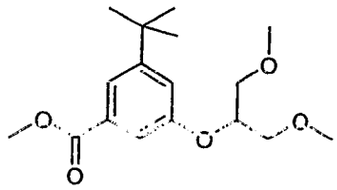


Methyl 3-tert-butyl-5-hydroxymethylbenzoate (3.5 g) was alkylated analogously to O5.059 with 2-(2-bromoethoxy)tetrahydropyran (3.95 g). However, silica gel chromatography (n-heptane/EA 4:1) was carried out for purification. 2.28 g of the title compound were obtained.

^{1}H NMR (500 MHz, DMSO-d6) [ppm] (representative signals): 7.87 (1 H); 7.76 (1 H); 7.63 (1 H); 4.60 (1 H, -O-C(-C)H-O-); 4.57 (2 H)

O5.072

Methyl 3-tert-butyl-5-(2-methoxy-1-methoxymethylethoxy)benzoate



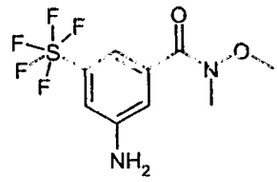
Methyl 3-tert-butyl-5-hydroxybenzoate (O6.043; 2.28 g) and 2-methoxy-1-methoxymethyl-ethyl methanesulfonate (2.93 g) were dissolved in DMF (50 ml), and cesium carbonate (4.82 g) was added. After stirring at 50°C for 6 h, the mixture was left to stand overnight. After stirring at 50°C for 4 further hours, one further eq. of cesium carbonate and one further eq. of the mesylate were added, and the mixture was stirred at 50°C for a further 4 h and left to stand overnight. Then the mixture was stirred at 50°C for a further 8 h and left to stand for 6 days, and then a further 0.5 eq. of cesium carbonate and mesylate was added. After stirring at 50°C for a further 8 h, the mixture was left to stand for 5 days, then the DMF was drawn

off and the residue was taken up with DCM/water. The DCM phase was removed and concentrated. The residue was purified using silica gel (120 g cartridge, n-heptane/MTB ether gradient 0-50% within 60 min). 2.05 g of the title compound were obtained.

LC-MS rt: 1.72 min $[M+H-HOCH_3]^+$: 279.1 (met. a)

O5.075

3-Amino-N-methoxy-N-methyl-5-pentafluorosulfanylbenzamide

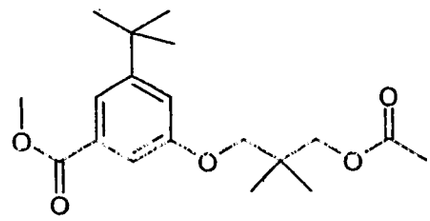


N-Methoxy-N-methyl-5-nitro-3-pentafluorosulfanylbenzamide (O6.075; 4.2 g) was dissolved in methanol (120 ml), and Raney nickel (about 700 mg) was added. With a hydrogen balloon attached, hydrogenation was effected on a magnetic stirrer. After 5 h, the catalyst was filtered off and washed with methanol. The filtrate was concentrated under reduced pressure and the residue was purified by means of preparative chromatography. The product-containing fractions were combined, freed of the acetonitrile, basified with sodium hydrogencarbonate solution and extracted three times with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated. 1.73 g of the desired compound were obtained.

LC-MS rt: 1.27 min $[M+H]^+$: 307.0 (met. a)

O5.086

Methyl 3-(3-acetoxy-2,2-dimethylpropoxy)-5-tert-butylbenzoate

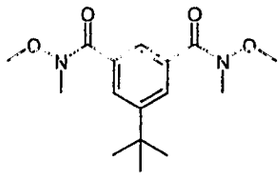


Methyl 3-tert-butyl-5-hydroxybenzoate (O6.043; 1.79 g) was reacted with 3-bromo-2,2-dimethylpropyl acetate, worked up and purified analogously to O2.85. 1.01 g of the title compound were obtained.

LC-MS rt: 2.01 min $[M+H]^+$: 337.1 (met. a)

O5.106

5-tert-Butyl-N,N'-dimethoxy-N,N'-dimethylisophthalamide



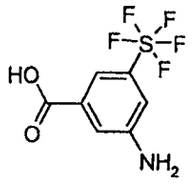
In a 4 l three-neck flask with reflux condenser and mechanical stirrer, 5-*tert*-butylisophthalic acid (300 g, 1.35 mol) was added to thionyl chloride (1.60 l, 2.62 kg, 22.0 mol). The resulting suspension was stirred at 80°C. After 4 h, a clear solution had formed and the solvent was distilled off. The residue was then dried under reduced pressure and then suspended in dichloromethane (1.5 l). This suspension was cooled to 0°C and *N,O*-dimethylhydroxylamine hydrochloride (395 g, 4.05 mol) was added. Subsequently, triethylamine (1.50 l, 1.09 kg, 10.8 mol) was slowly added dropwise such that the temperature did not exceed 15°C. Once the mixture had been stirred at RT for 16 h, water was added (1 l). The phases were separated and the organic phase washed with saturated NH_4Cl solution (2 × 500 ml), saturated $NaHCO_3$ solution (2 × 500 ml) and saturated NaCl solution (1 × 500 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The product was obtained as a white solid (405 g).

LC-MS rt: 1.22 min $[M+H]^+$: 309 (met. a)

O6

O6.007

3-Amino-5-pentafluorosulfanylbenzoic acid



3-Pentafluorosulfanylbenzoic acid (15 g) was dissolved in fuming nitric acid (120 ml) and stirred at RT with exclusion of moisture. Then concentrated sulfuric acid (7.5 ml) was added and the mixture was stirred at 75°C. After stirring at 75°C for 8 h, the mixture was left to stand overnight, then further sulfuric acid (1.5 ml) was added and the mixture was heated to

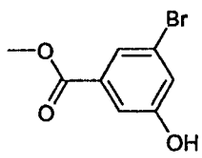
75°C while stirring for 8 h. After being left to stand overnight, the mixture was added to ice-water and stirred for 2 h. Then the precipitate was filtered off with suction and dried under high vacuum. 13.7 g of 3-pentafluorosulfanyl-5-nitrobenzoic acid were obtained.

Subsequently, the 3-pentafluorosulfanyl-5-nitrobenzoic acid (5 g) was dissolved in methanol (300 ml), Raney nickel (about 750 mg) was added and hydrogenation was effected under a hydrogen atmosphere (hydrogen balloon). After 3 h, the catalyst was filtered off and the filter residue was washed thoroughly with methanol. The filtrate was concentrated and dried. The residue was purified using silica gel (2 x 50 g cartridge, n-heptane/EA gradient of 0-100% within 60 min). 3.9 g of the title compound were obtained.

^{1}H NMR (400 MHz, DMSO-d_6) [ppm]: 13.30 (1 H); 7.37 (2 H); 7.23 (1 H); 5.98 (2 H)

O6.032

Methyl 3-bromo-5-hydroxybenzoate

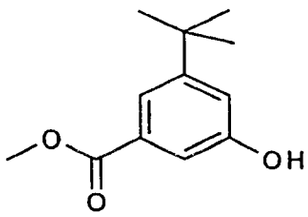


3-Bromo-5-hydroxybenzoic acid (3 g) was converted to the title compound analogously to O6.043. 2.52 g were obtained.

^{1}H NMR (500 MHz, DMSO-d_6) [ppm]: 10.40 (1 H); 7.47 (1 H); 7.33 (1 H); 7.22 (1 H); 3.84 (3 H)

O6.043

Methyl 3-tert-butyl-5-hydroxybenzoate



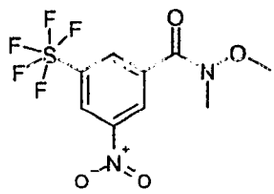
3-tert-Butyl-5-hydroxybenzoic acid (O7.043; 1.93 g) was dissolved in methanol (20 ml), and thionyl chloride (0.937 ml) was slowly added dropwise while stirring. After stirring at 65°C for 1 h, the mixture was dried, the residue was taken up in DCM, and the solution was

washed with saturated sodium hydrogencarbonate solution, dried over MgSO4, filtered and concentrated by rotary evaporation. 2.19 g of the title compound were obtained.

LC-MS rt: 1.44 min $[M+H]^+$: 209.2 (met. a)

O6.075

N-Methoxy-N-methyl-5-nitro-3-pentafluorosulfanylbenzamide



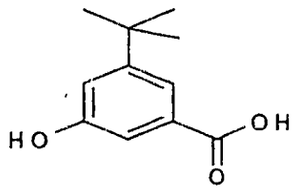
3-Pentafluorosulfanylbenzoic acid (5.0 g) was dissolved in fuming nitric acid (20 ml) and stirred at RT with exclusion of moisture. Then concentrated sulfuric acid (3 ml) was added and the mixture was stirred at 75°C. After stirring at 75°C for 5 h, further sulfuric acid (2 ml) was added and the mixture was stirred at 75°C for a further 2 h. After being left to stand overnight, the mixture was poured onto ice-water and stirred for 2 h. Then the precipitate was filtered off with suction and dried under high vacuum. 4.2 g of 3-pentafluorosulfanyl-5-nitro-benzoic acid were obtained. A further 900 mg were obtained from the mother liquor after extracting three times with methylene chloride, drying the combined methylene chloride phases over magnesium sulfate and concentrating the solvent. Subsequently, 4.0 g of the 3-pentafluorosulfanyl-5-nitrobenzoic acid were dissolved in thionyl chloride (25 ml) while stirring and kept under reflux with exclusion of moisture for 10 h. After standing overnight at RT, excess thionyl chloride was removed under reduced pressure, and the residue obtained was dissolved in dichloromethane (50 ml) and admixed while stirring with N,O-dimethyl-hydroxylamine x HCl (1.25 g) and diethylisopropylamine (1.66 g). After stirring at RT for 1 h, the mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate and washed five times with water. The organic phase was dried over magnesium sulfate, filtered and concentrated. The 4.2 g of crude product obtained were used directly in the next stage.

LC-MS rt: 1.50 min $[M+H]^+$: 337.0 (met. a)

O7

O7.043

3-tert-Butyl-5-hydroxybenzoic acid

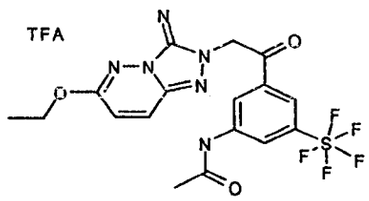


3-Bromo-5-tert-butylbenzoic acid (5 g) was dissolved in THF (180 ml), and n-butyllithium (18.7 ml, 2.5 M in hexane) was added dropwise under argon and at -75°C, and stirred for a further 30 min. Then trimethyl borate (6.63 ml) was added dropwise and the mixture was allowed to come to RT within 1 h. Thereafter, sodium hydroxide (0.778 g), dissolved in 2 ml of water, and hydrogen peroxide (12.89 ml, 30 %) were added in succession. After stirring at RT for 3 h, the mixture was left to stand over the weekend. Then water and EA were added, the mixture was adjusted to pH 3 with 1 N hydrochloric acid and the EA phase was removed. This phase was washed three times with water, dried, filtered and concentrated. The residue was purified using silica gel (120 g cartridge, n-heptane/MtB ether gradient of 0-50% in 60 min). 1.94 g of the title compound were obtained.

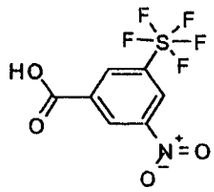
LC-MS rt: 1.18 min $[M+H]^+$: 195.1 (met. a)

Example 1

N-[3-[2-(6-Ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)acetyl]-5-(pentafluorosulfanyl)phenyl]acetamide as the trifluoroacetic acid salt



a) 3-Nitro-5-pentafluorosulfanylbenzoic acid

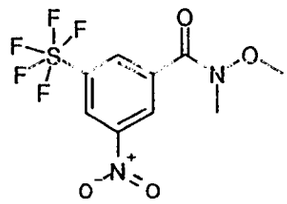


3-Pentafluorosulfanylbenzoic acid (5.0 g) was dissolved in fuming nitric acid (20 ml) and stirred at RT with exclusion of moisture. Then concentrated sulfuric acid (3 ml) was added

and the mixture was stirred at 75 °C. After stirring at 75°C for 5 h, further sulfuric acid (1.5 ml) was added and, after stirring at 75°C for 2 h, left to stand overnight. Then the mixture was added to ice-water and stirred for 2 h. The precipitate formed was filtered off with suction and dried under high vacuum. 4.2 g of 3-pentafluorosulfanyl-5-nitrobenzoic acid were obtained. A further 900 mg were obtained from the mother liquor after extracting three times with methylene chloride, drying the combined methylene chloride phases over magnesium sulfate and concentrating the solvent. The precipitate was used in the next stage without further purification.

^{1}H NMR (400 MHz, DMSO-d_6) [ppm]: 8.82 (1 H); 8.80 (1 H); 8.62 (1 H)

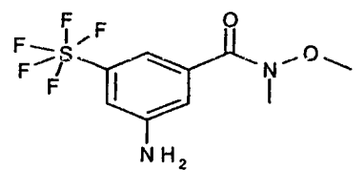
b) N-Methoxy-N-methyl-5-nitro-3-pentafluorosulfanylbenzamide



3-Nitro-5-pentafluorosulfanylbenzoic acid (4.0 g) was dissolved in thionyl chloride (25ml) while stirring and kept under reflux with exclusion of moisture for 10 h. After standing overnight, excess thionyl chloride was removed under reduced pressure at RT, and the resulting residue was dissolved in dichloromethane (50 ml) and admixed with N,O-dimethyl-hydroxylamine hydrochloride (1.25 g) and diethylisopropylamine (1.66 g) while stirring. After stirring at RT for 1 h, the mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate and washed 5 times with water. The organic phase was dried over magnesium sulfate, filtered and concentrated. The resulting crude product (4.2 g) was used directly in the next stage.

LC-MS rt: 1.50 min $[M+H]^+$: 337.0 (met. a)

c) 3-Amino-N-methoxy-N-methyl-5-pentafluorosulfanylbenzamide

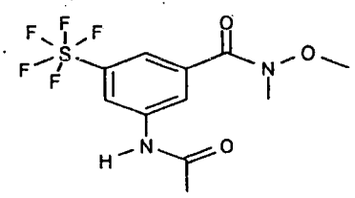


N-Methoxy-N-methyl-5-nitro-3-pentafluorosulfanylbenzamide (4.2 g) was dissolved in

methanol (120 ml), and Raney nickel (approx. 700 mg) was added. With a hydrogen balloon attached, hydrogenation was effected on a magnetic stirrer. After 5 h, the catalyst was filtered off and washed with methanol. The filtrate was concentrated under reduced pressure and the residue was purified by means of preparative chromatography. The product-containing fractions were combined, freed of the acetonitrile, basified with sodium hydrogencarbonate solution and extracted three times with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated. 1.73 g of the desired compound were obtained.

LC-MS rt: 1.27 min $[M+H]^+$: 307.0 (met. a)

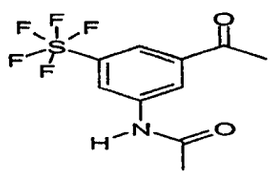
d) 3-Acetylamino-N-methoxy-N-methyl-5-(pentafluorosulfanyl)benzamide



3-Amino-N-methoxy-N-methyl-5-pentafluorosulfanylbenzamide (1.2 g) was dissolved in methylene chloride (15 ml), and triethylamine (0.7 ml) followed by acetic anhydride (1.75 ml) were added while stirring with exclusion of moisture. After stirring at RT for 3 h, water and saturated sodium hydrogencarbonate solution were added, the phases were separated and the methylene chloride phase was washed three times more with water, dried over magnesium sulfate, filtered and concentrated. The resulting product (1.3 g) was used in the next stage without further purification.

LC-MS rt: 1.26 min $[M+H]^+$: 349.0 (met. a)

e) N-[3-Acetyl-5-(pentafluorosulfanyl)phenyl]acetamide

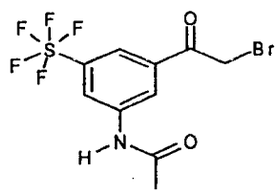


3-Acetylamino-N-methoxy-N-methyl-5-(pentafluorosulfanyl)benzamide (1.2 g) was dissolved in absolute THF (30 ml) and stirred at 0°C with lithium hexamethyldisilazide (721 µl; density: 0.8 g/l; 23% in *tert*-butyl methyl ether) for 30 min. At 0°C, methylmagnesium bromide (2.87 ml, 3 M in diethyl ether) was then added dropwise while

stirring. After stirring at RT for 2.5 h, further methylmagnesium bromide (1 ml, 3 M in diethyl ether) was added and the mixture was stirred again for 2.5 h. For workup, 1 N hydrochloric acid was added dropwise while cooling with ice, followed by water and ethyl acetate. The organic phase was removed and the water phase was extracted twice more with ethyl acetate. The combined ethyl acetate phases were dried over sodium sulfate, filtered and concentrated. The crude product (1.03 g) was combined with a crude product prepared in the same way (75 mg) and purified using silica gel with dichloromethane-methanol as the eluent. 860 mg of the desired compound were obtained.

LC-MS rt: 1.34 min $[M+H]^+$: 304.0 (met. a)

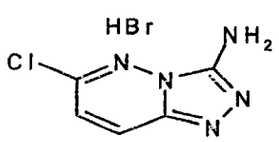
f) N-[3-(2-Bromoacetyl)-5-(pentafluorosulfanyl)phenyl]acetamide (O1.001)

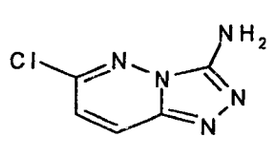


N-[3-Acetyl-5-(pentafluorosulfanyl)phenyl]acetamide (859 mg) was dissolved in a mixture of methanol (10 ml) and THF (10 ml) and phenyltrimethylammonium tribromide (1.065 g) was added in portions while stirring. After stirring at RT for 2 h, the mixture was heated to 40°C for a further 3 h. After cooling, the reaction mixture was added to 2 N sulfuric acid and the aqueous phase was extracted 3 times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated. The crude product was purified using silica gel with ethyl acetate/heptane as the eluent. 480 mg of the desired compound were obtained.

LC-MS rt: 1.47 min $[M+H]^+$: 382.0 (met. a)

g) 6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine as the hydrobromide (W2.001) and 6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W2.001a)





(6-Chloropyridazin-3-yl)hydrazine (1 g) was dissolved in a mixture of ethanol (22.5 ml) and water (9 ml) at RT while stirring. Thereafter, cyanogen bromide (2.8 ml, 5 M in acetonitrile) was added dropwise while stirring. After stirring for 6 h and leaving to stand overnight, the

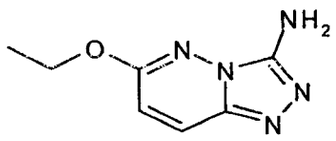
precipitate was filtered off with suction and dried. In this way, 1.14 g of the desired product were obtained as the hydrobromide.

LC-MS rt: 0.24 min $[M+H]^+$: 170.1 (met. a)

Further product was obtained in the form of the free base, by basifying the mother liquor with saturated potassium carbonate solution. The precipitate formed was filtered off with suction and dried (326 mg).

LC-MS rt: 0.24 min $[M+H]^+$: 170.1 (met. a)

h) 6-Ethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine



6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine hydrobromide (W2.001; 1.1 g) was taken up in a large amount of water and alkalized with saturated potassium carbonate solution. The solid which precipitated out was filtered off with suction and dried (388 mg). Repeated extraction of the mother liquor with dichloromethane, drying of the combined organic phases over sodium sulfate, filtration and concentration afforded a further 228 mg of product in total. The resulting free base (616 mg) was dissolved in absolute ethanol (40 ml) and admixed with solid sodium ethoxide (990 mg) in portions. After stirring at 55°C for 2 h, water was added and the aqueous phase was extracted three times with dichloromethane. The combined extracts were dried over sodium sulfate, filtered and concentrated. 709 mg of the desired compound were obtained. LC-MS rt: 0.51 min $[M+H]^+$: 180.1 (met. a)

i) N-[3-[2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)acetyl]-5-(pentafluorosulfanyl)phenyl]acetamide as the trifluoroacetic acid salt

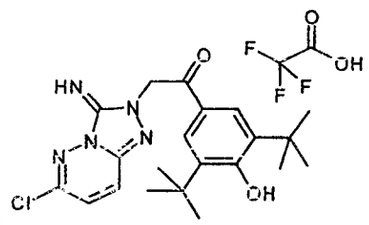
6-Ethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W1.001; 40 mg) was initially charged in absolute DMF (3.5 ml) while stirring, and N-[3-(2-bromoacetyl)-5-(pentafluorosulfanyl)-phenyl]acetamide (O1.001; 94 mg), dissolved in absolute DMF (1.5 ml), was added dropwise. After stirring at RT for 5 h and leaving to stand overnight, the solvent was drawn off and the residue was purified by means of preparative chromatography (met. A). The product-containing fractions were combined, freed of the acetonitrile and freeze-dried (90 mg). To remove the cationic isomer, a further purification using silica gel with a

dichloromethane/methanol gradient was carried out. The fractions of the desired product, which elutes first, were combined and dried. The residue was then purified further by means of preparative chromatography (met. A). The product-containing fractions were combined, freed of the acetonitrile and freeze-dried. 42 mg of the desired compound were obtained.

LC-MS rt: 1.12 min $[M+H]^+$: 481.0 (met. a)

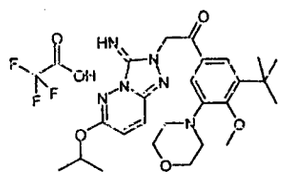
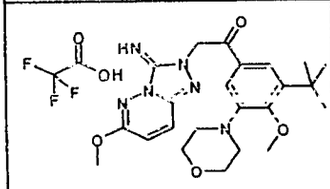
Example 2

2-(6-chloro-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(3,5-di-tert-butyl-4-hydroxyphenyl)ethanone



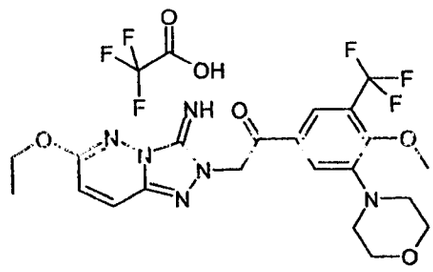
6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamin (W2.001a; 30 mg) was initially charged in DMF (3.5 ml) at RT while stirring, and 2-bromo-1-(3,5-di-tert-butyl-4-hydroxyphenyl)ethanone (O1.002; 58 mg) predissolved in DMF (0.5 ml) was added dropwise. The reaction mixture was stirred at RT for 30 min and was then heated to 60°C for 5 h. After standing overnight, the solvent was removed under reduced pressure and the residue was purified by means of preparative HPLC (met. A). The clean product fractions were combined, freed of the acetonitrile under reduced pressure and freeze-dried. 28 mg of the title compound were obtained. LC-MS rt: 1.28 min $[M+H]^+$: 416.1 (met. a)

The following were obtained analogously to example 2:

	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-isopropoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt (16 mg)					
Ex. 3		W 1.003 15 mg	O 1.003 29 mg	LC-MS rt [min] 1.35	$[M+H]^+$ 483.3 (met. a)	
	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-methoxy-[1,2,4]-triazolo[4,3-b]pyridazin-2-yl)ethanone ethanone trifluoroacetic acid salt (34 mg)					
Ex. 4		W 1.002 30 mg	O 1.003 74 mg	LC-MS rt [min] 1.24	$[M+H]^+$ 455.1 (met. a)	

Example 5

2-(6-Ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(4-methoxy-3-morpholin-4-yl-5-trifluormethylphenyl)ethanone trifluoroacetic acid salt

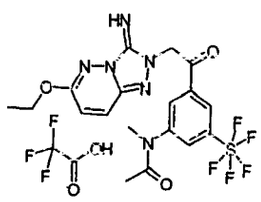
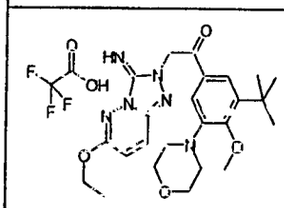


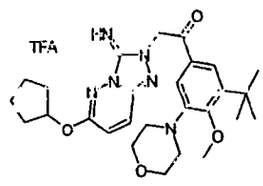
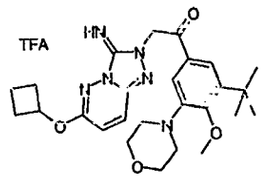
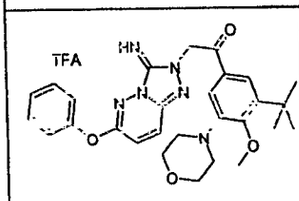
6-Ethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W1.001; 10 mg) was initially charged in DMF (3.5 ml) at RT while stirring, and 2-bromo-1-(4-methoxy-3-morpholin-4-yl-5-trifluoro-methylphenyl)ethanone (O1.004; 21 mg) predissolved in DMF (1.5 ml) was added dropwise.

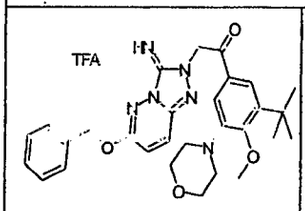
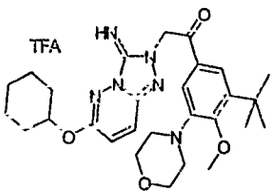
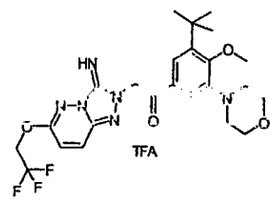
The reaction mixture was stirred at RT for 2 h. After standing overnight, the solvent was removed under reduced pressure and the residue was purified by means of preparative HPLC (met. A). The clean product fractions were combined, freed of the acetonitrile under reduced pressure and freeze-dried. The title compound contaminated with 1-substitution product was purified using silica gel with a dichloromethane/methanol gradient. The clean product fractions were dried, taken up with a little acetonitrile/water+0.05% TFA and freeze-dried. 7 mg of the title compound were obtained.

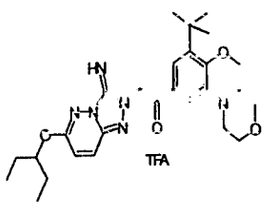
LC-MS rt: 1.20 min $[M+H]^+$: 481.1 (met. a)

The following were obtained analogously to the above examples:

Ex. 6	N-[3-[2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)acetyl]-5-(pentafluorosulfanyl)phenyl]-N-methylacetamide trifluoroacetic acid salt (6 mg)					
		W 1.001 15 mg	O 1.005 29 mg	LC-MS rt [min] 1.10	$[M+H]^+$ 495.0 (met. a)	analogous to ex. 5
Ex. 7	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt (15 mg)					
		W 1.001 30 mg	O 1.003 62 mg	LC-MS rt [min] 1.34	$[M+H]^+$ 469.2 (met. a)	analogous to ex. 2

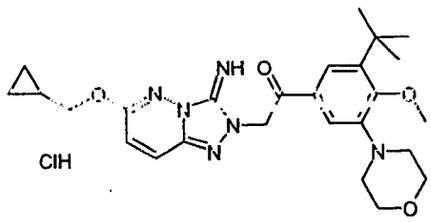
Ex. 8	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclopentyloxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt (4 mg)					
		W 1.007 15 mg	O 1.003 18 mg	LC-MS rt [min] 1.44	$[M+H]^+$ 509.2 (met. a)	analogous to ex. 5, but in the presence of 7.3 µl of TEA
Ex. 9	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclobutoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt (41 mg)					
		W 1.004 15 mg	O 1.003 18 mg	LC-MS rt [min] 1.40	$[M+H]^+$ 495.2 (met. a)	analogous to ex. 5
Ex. 10	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-phenoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt (29 mg)					
		W 1.013 18 mg	W 1.003 32 mg	LC-MS rt [min] 1.35	$[M+H]^+$ 517.3 (met. a)	analogous to ex. 5

Ex. 11	2-(6-benzyloxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)ethanone trifluoroacetic acid salt (27 mg)					
		W 1.005 20 mg	O 1.003 34 mg	LC-MS rt [min] 1.40	$[M+H]^+$ 531.2 (met. a)	analogous to ex. 5
Ex. 12	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclohexyloxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt (5 mg)					
		W 1.006 20 mg	O 1.003 18 mg	LC-MS rt [min] 1.54	$[M+H]^+$ 523.3 (met. a)	analogous to ex. 5, but in the presence of 7.2 µl of TEA
Ex. 13	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[3-imino-6-(2,2,2-trifluoro-ethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt (25 mg)					
		W 1.014 23 mg	O 1.003 39 mg	LC-MS rt [min] 1.33	$[M+H]^+$ 523.2 (met. a)	analogous to ex. 5

	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt (14 mg)					
Ex. 14		W 1.008 20 mg	O 1.003 37 mg	LC-MS rt [min] 1.48	$[M+H]^+$ 511.2 (met. a)	analogous to ex. 5

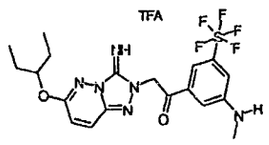
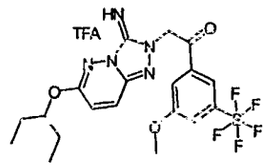
Example 15

1-(3-tert-Butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclopropylmethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride



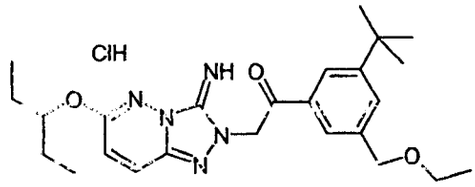
6-Cyclopropylmethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W1.009; 350 mg) was initially charged in DMF (5 ml) at RT while stirring, and 2-bromo-1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)ethanone (O1.003; 631 mg) predissolved in DMF (5 ml) was added dropwise. The reaction mixture was stirred at RT for 14 h. Then the solvent was removed under reduced pressure and the residue was purified using silica gel (40 g cartridge, dichloromethane/ethanol gradient of 0–40% in 60 min). The product was taken up with a little acetonitrile, diluted with water and, after addition of 2 eq. of HCl, freeze-dried. 500 mg of the title compound were obtained. LC-MS rt: 1.37 min $[M+H]^+$: 495.2 (met. a)

The following were obtained analogously to the above examples:

Ex. 16	2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methylamino-5-(pentafluorosulfanyl)phenyl]ethanone trifluoroacetic acid salt (11 mg)					
		W 1.008 19 mg	O 1.006 30 mg	LC-MS rt [min] 1.35	$[M+H]^+$ 495.1 (met. a)	analogous to ex. 5
Ex. 17	2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone trifluoroacetic acid salt (23 mg)					
		W 1.008 25 mg	O 1.007 40 mg	LC-MS rt [min] 1.35	$[M+H]^+$ 496.1 (met. a)	analogous to ex. 5

Example 18

1-(3-tert-butyl-5-ethoxymethylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone hydrochloride

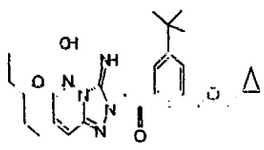
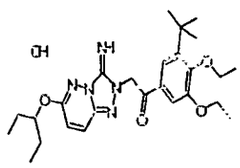


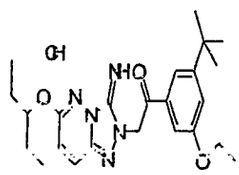
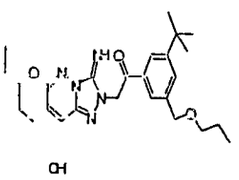
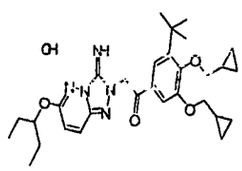
6-(1-Ethylpropoxy)-[1,2,4]triazolo[4,3-b]pyridazin-3-ylamine (W1.008; 205 mg) was initially charged in DMF (5 ml) at RT while stirring, and 2-bromo-1-(3-tert-butyl-5-ethoxy-methylphenyl)ethanone (O1.008; 290 mg) was added dropwise predissolved in DMF (5 ml). The reaction mixture was stirred at RT for 14 h. Then the solvent was removed under reduced pressure and the residue was purified using silica gel (40 g cartridge, dichloromethane/

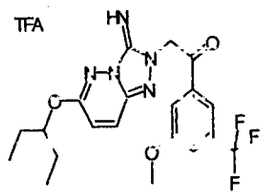
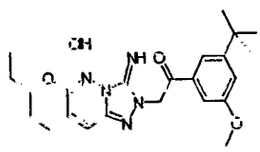
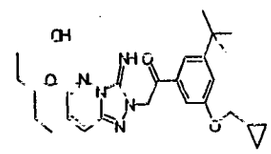
ethanol gradient of 0-40% in 60 min). The still contaminated product was subsequently purified by means of preparative HPLC. The clean product fractions were combined, freed of the acetonitrile under reduced pressure and freeze-dried. The residue was dissolved in water and acetonitrile and, after addition of 3 eq. of HCl, freeze-dried. 72 mg of the title compound were obtained.

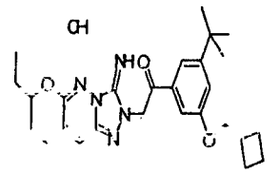
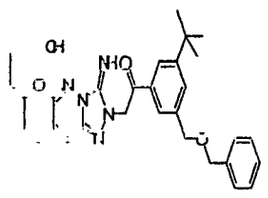
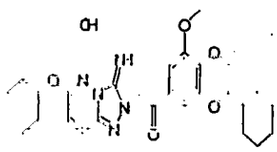
LC-MS rt: 1.44 min $[M+H]^+$: 454.5 (met. a)

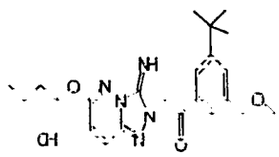
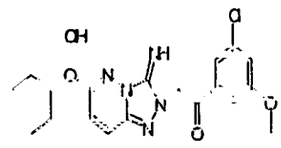
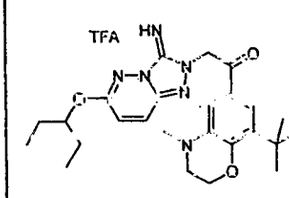
The following were prepared analogously to the above examples:

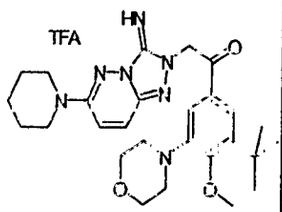
	1-(3-tert-butyl-5-cyclopropylmethoxymethylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (155 mg)					
Ex. 19		W 1.008 198 mg	O 1.009 304 mg	LC-MS rt [min] 3.36	$[M+H]^+$ 480.2 (met. d)	analogous to ex. 18
	1-(3-tert-butyl-4,5-diethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (96 mg)					
Ex. 20		W 1.008 130 mg	O 1.010 202 mg	LC-MS rt [min] 3.47	$[M+H]^+$ 484.1 (met. d)	analogous to ex. 18

Ex. 21	1-(3-tert-butyl-5-ethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (114 mg)					
		W 1.008 140 mg	O 1.011 189 mg	LC-MS rt [min] 1.46	$[M+H]^+$ 440.5 (met. a)	analogous to ex. 18
Ex. 22	1-(3-tert-butyl-5-propoxymethylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (92 mg)					
		W 1.008 180 mg	O 1.012 266 mg	LC-MS rt [min] 3.00	$[M+H]^+$ 468.1 (met. d)	analogous to ex. 18
Ex. 23	1-(3-tert-butyl-4,5-bis(cyclopropylmethoxy)phenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (112 mg)					
		W 1.008 165 mg	O 1.013 295 mg	LC-MS rt [min] 1.662	$[M+H]^+$ 536.5 (met. a)	analogous to ex. 18

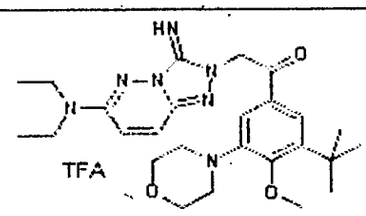
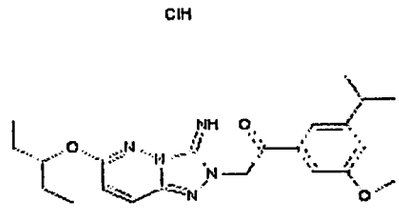
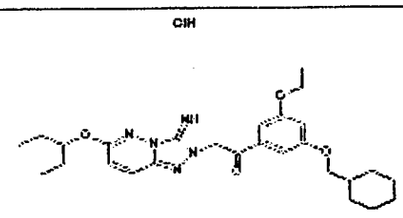
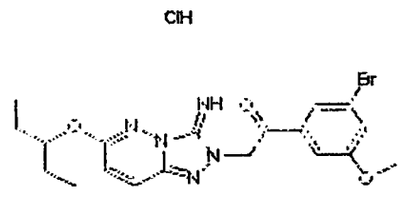
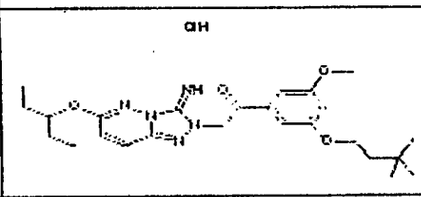
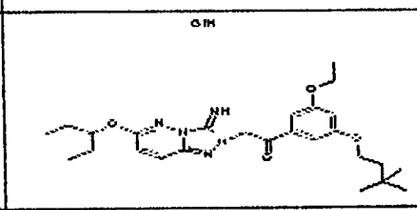
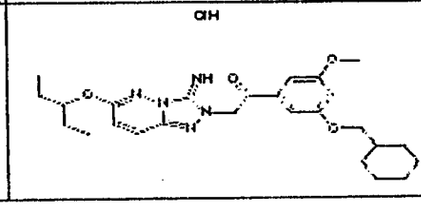
Ex. 24	2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-(3-methoxy-5-trifluormethylphenyl)ethanone trifluoroacetic acid salt (31 mg)					
		W 1.008 25 mg	O 1.014 34 mg	LC-MS rt [min] 1.33	$[M+H]^+$ 438.1 (met. a)	analogous to ex. 2
Ex. 25	1-(3-tert-butyl-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (176 mg)					
		W 1.008 200 mg	O 1.015 258 mg	LC-MS rt [min] 3.18	$[M+H]^+$ 426.1 (met. d)	analogous to ex. 18
Ex. 26	1-(3-tert-butyl-5-cyclopropylmethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (152 mg)					
		W 1.008 180 mg	O 1.016 265 mg	LC-MS rt [min] 3.44	$[M+H]^+$ 466.3 (met. d)	analogous to ex. 18

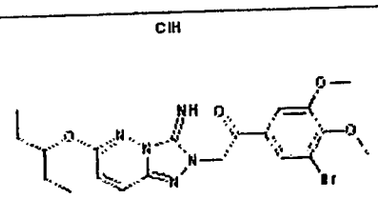
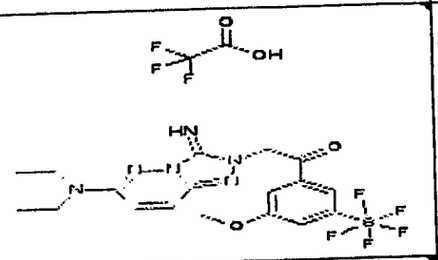
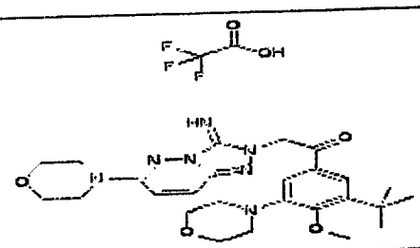
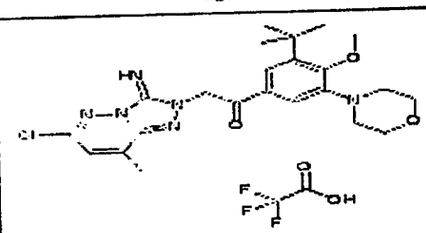
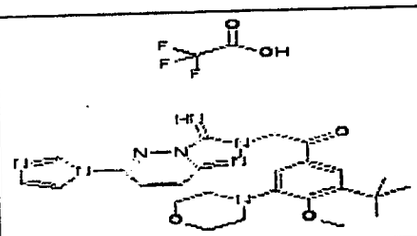
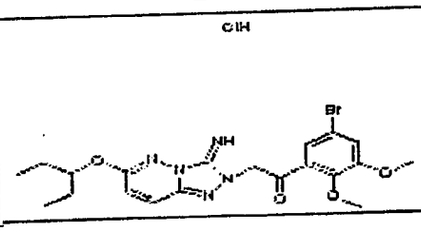
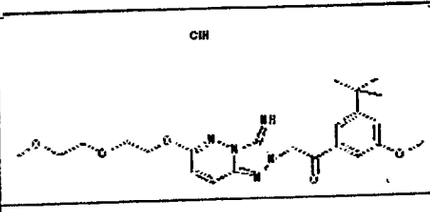
Ex. 27	1-(3-tert-butyl-5-cyclobutylmethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (137 mg)					
		W 1.008 180 mg	O 1.017 276 mg	LC-MS rt [min] 1.58	$[M+H]^+$ 480.5 (met. a)	analogous to ex. 18
Ex. 28	1-(3-benzyloxymethyl-5-tert-butylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (183 mg)					
		W 1.008 200 mg	O 1.018 339 mg	LC-MS rt [min] 1.53	$[M+H]^+$ 516.5 (met. a)	analogous to ex. 18
Ex. 29	1-(3-cyclohexylmethoxy-4,5-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (76 mg)					
		W 1.008 75 mg	O 1.019 126 mg	LC-MS rt [min] 1.50	$[M+H]^+$ 512.5 (met. a)	analogous to ex. 18

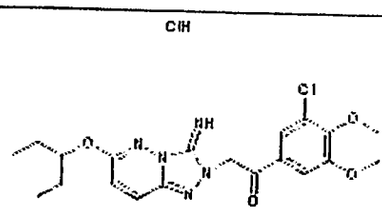
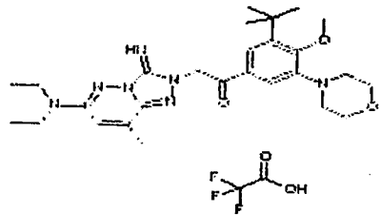
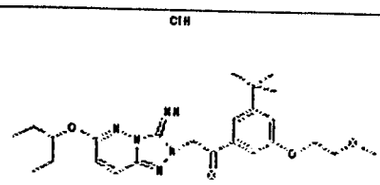
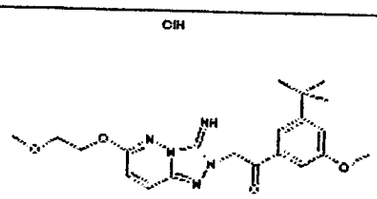
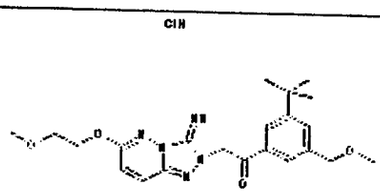
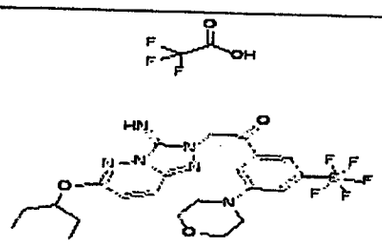
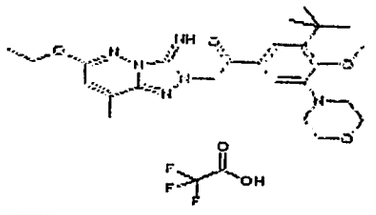
Ex. 30	2-(6-butoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(3-tert-butyl-5-methoxymethylphenyl)ethanone hydrochloride (83 mg)					
		W 1.010 240 mg	O 1.020 347 mg	LC-MS rt [min] 1.33	$[M+H]^+$ 426.3 (met. a)	analogous to ex. 18
Ex. 31	1-(3-chloro-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride (169 mg)					
		W 1.008 250 mg	O 1.021 298 mg	LC-MS rt [min] 1.28	$[M+H]^+$ 404.2 (met. a)	analogous to ex. 18
Ex. 32	1-(8-tert-butyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-[6-(1-ethyl-propoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt (13 mg)					
		W 1.008 25 mg	O 1.022 37 mg	LC-MS rt [min] 1.43	$[M+H]^+$ 467.3 (met. a)	analogous to ex. 5

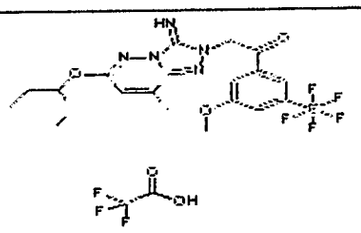
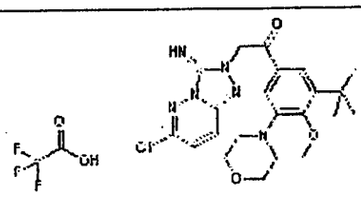
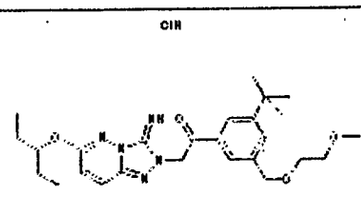
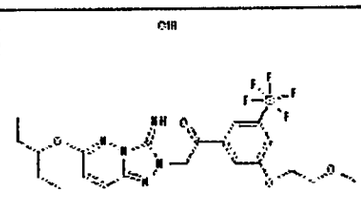
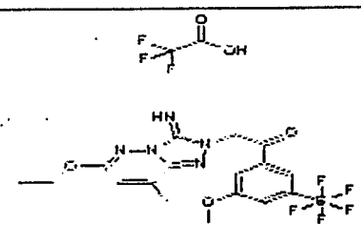
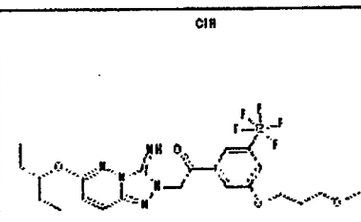
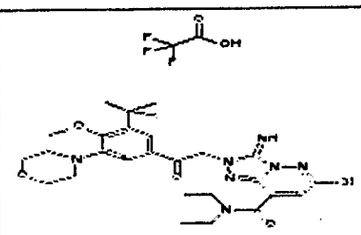
Ex.	1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-piperidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt (30 mg)					
33		W 1.020 25 mg	O 1.003 42 mg	LC-MS rt [min] 1.37	$[M+H]^+$ 508.3 (met. a)	analogous to ex. 5

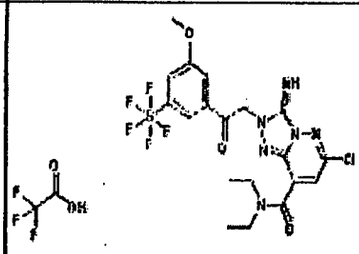
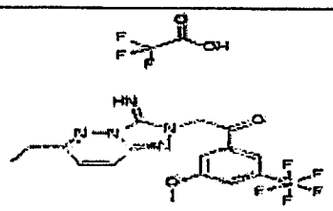
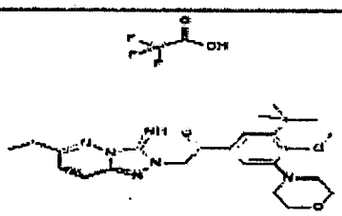
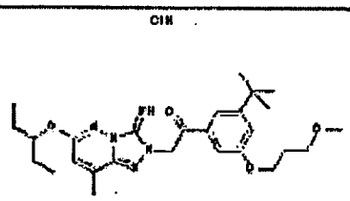
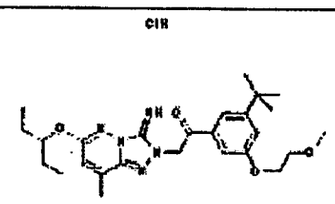
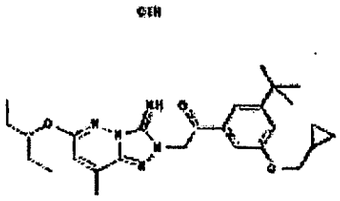
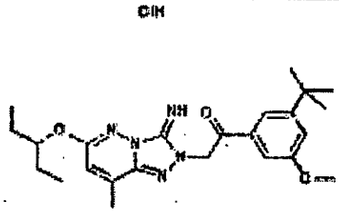
Analogously to the above methods, the W1 and O1 base structures were used to prepare and characterize the following examples:

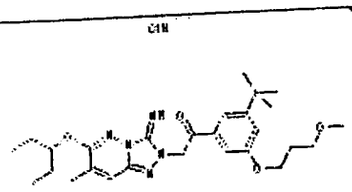
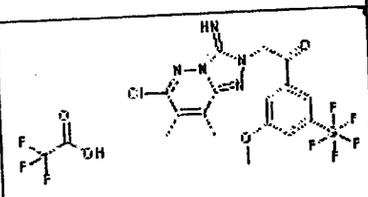
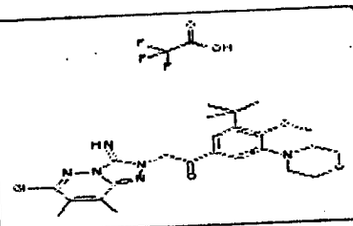
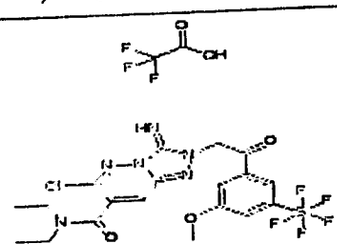
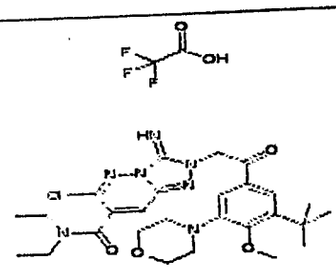
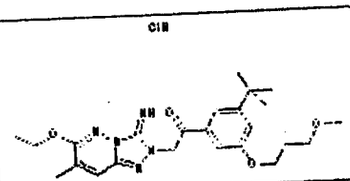
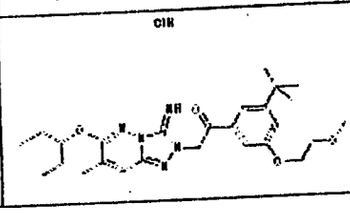
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 034		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-diethylamino-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.37	496.3 (met. a)
Ex.: 035		2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-(3-isopropyl-5-methoxyphenyl)ethanone hydrochloride	1.36	412.3 (met. a)
Ex.: 036		1-(3-cyclohexylmethoxy-5-ethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.56	496.4 (met. a)
Ex.: 037		1-(3-bromo-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	.1.3	448.1 (met. a)
Ex.: 038		1-[3-(3,3-dimethylbutoxy)-5-methoxyphenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.52	470.4 (met. a)
Ex.: 039		1-[3-(3,3-dimethylbutoxy)-5-ethoxyphenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.56	484.4 (met. a)
Ex.: 040		1-(3-cyclohexylmethoxy-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.55	482.4 (met. a)

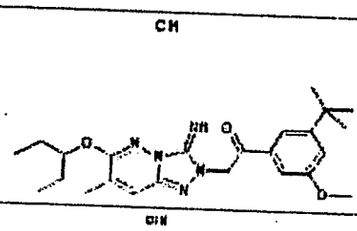
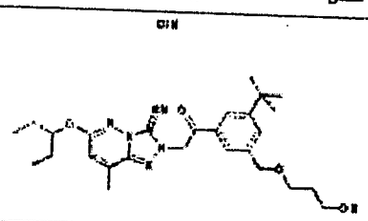
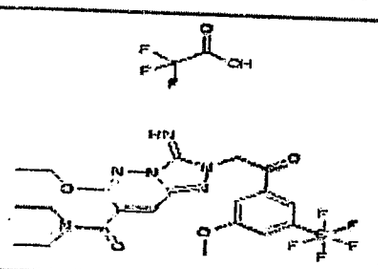
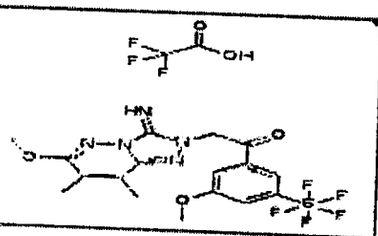
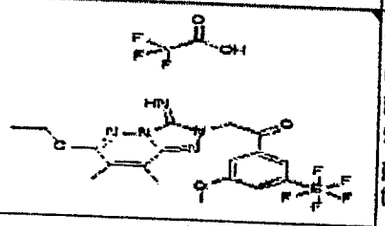
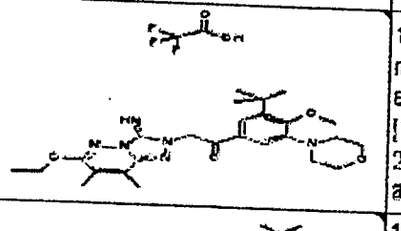
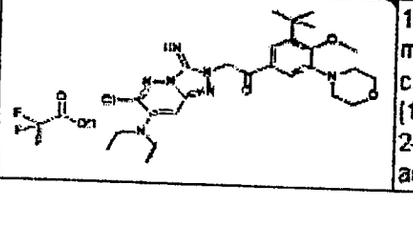
		Name	LC-MS rt [min]	[M+H]+
Ex.: 041		1-(3-bromo-4,5-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone hydrochloride	1.29	478.1 (met. a)
Ex.: 042		2-(6-diethylamino-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluoro-sulfanyl)phenyl]ethanone trifluoroacetic acid salt	1.29	481.1 (met. a)
Ex.: 043		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-morpholin-4-yl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.24	510.2 (met. a)
Ex.: 044		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.27	473.1 (met. a)
Ex.: 045		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-imidazol-1-yl-3-imino-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.12	491.1 (met. a)
Ex.: 046		1-(5-bromo-2,3-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.35	479.1 (met. a)
Ex.: 047		1-(3-tert-butyl-5-methoxy-phenyl)-2-[3-imino-6-[2-(2-methoxyethoxy)ethoxy]-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone hydrochloride	1.22	456.3 (met. a)

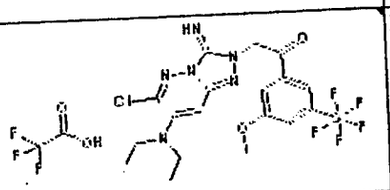
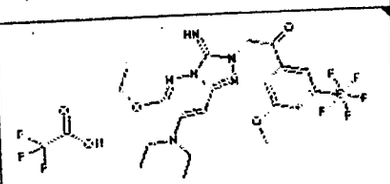
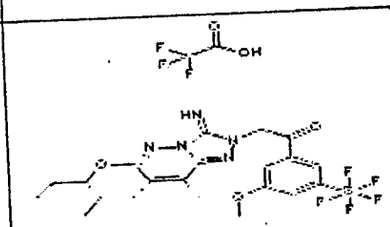
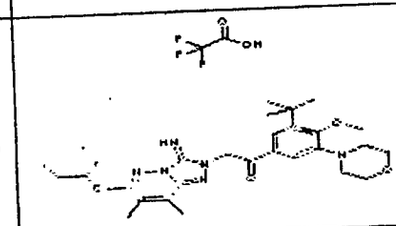
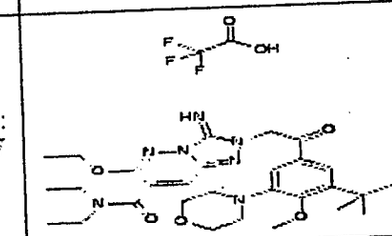
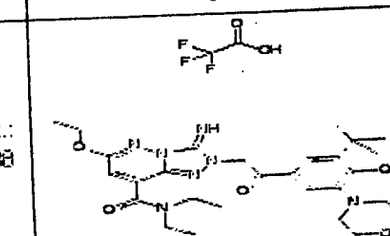
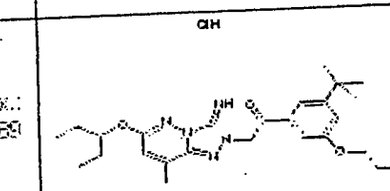
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 048		1-(3-chloro-4,5-dimethoxy-phenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone	1.3	434.1 (met. a)
Ex.: 049		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-diethylamino-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.42	510.4 (met. a)
Ex.: 050		1-[3-tert-butyl-5-(2-methoxy-ethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.42	470.3 (met. a)
Ex.: 051		1-(3-tert-butyl-5-methoxy-phenyl)-2-[3-imino-6-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.21	414.2 (met. a)
Ex.: 052		1-(3-tert-butyl-5-methoxy-methylphenyl)-2-[3-imino-6-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.21	428.3 (met. a)
Ex.: 053		2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-morpholin-4-yl-5-(pentafluorosulfanyl)phenyl]-ethanone trifluoroacetic acid salt	1.34	551.2 (met. a)
Ex.: 054		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.35	483.3 (met. a)

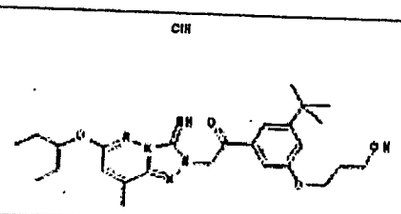
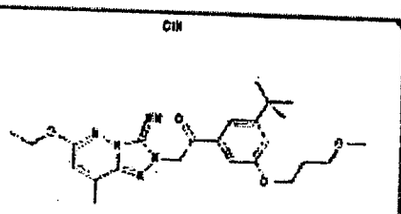
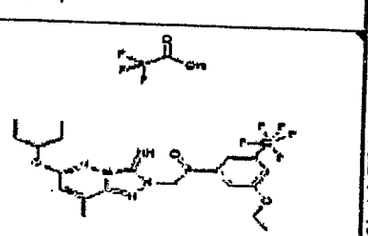
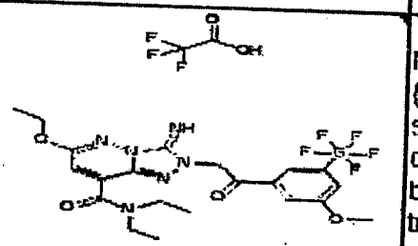
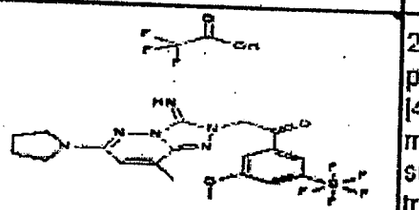
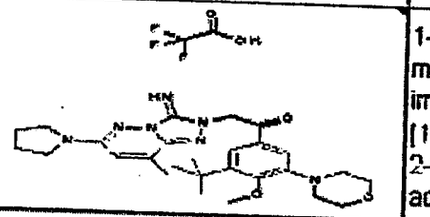
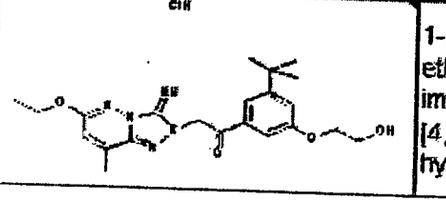
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 055		2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methoxy-5-(pentafluoro-sulfanyl)phenyl]ethanone trifluoroacetic acid salt	1.41	510.1 (met. a)
Ex.: 056		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-3-imino-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl)-ethanone trifluoroacetic acid salt	1.23	459.1 (met. a)
Ex.: 057		1-[3-tert-butyl-5-(2-methoxy-ethoxymethyl)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.38	484.4 (met. a)
Ex.: 058		2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-(2-methoxyethoxy)-5-(pentafluorosulfanyl)-phenyl]ethanone hydrochloride	1.38	484.4 (met. a)
Ex.: 059		2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-ethanone trifluoroacetic acid salt	1.26	468.0 (met. a)
Ex.: 060		2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-(3-methoxy-propoxy)-5-(pentafluoro-sulfanyl)phenyl]ethanone hydrochloride	0.95	554.2 (met. b)
Ex.: 061		N,N-diethyl-2-[2-(3-tert-butyl-4-methoxy-5-morpholin-4-yl-phenyl)-2-oxoethyl]-6-chloro-3-imino-2,3-dihydro-[1,2,4]triazolo[4,3-b]-pyridazine-8-carboxamide trifluoroacetic acid salt	1.29	558.3 (met. a)

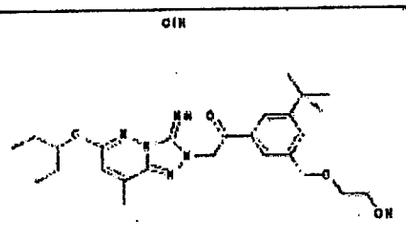
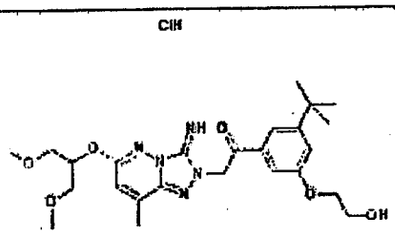
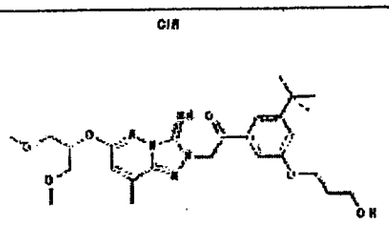
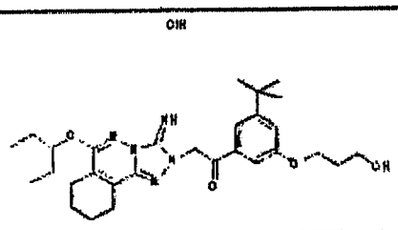
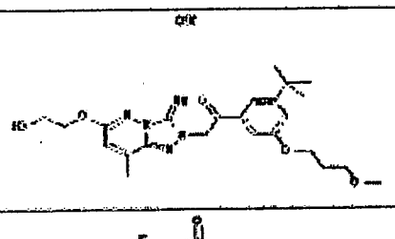
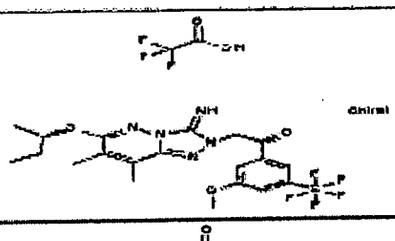
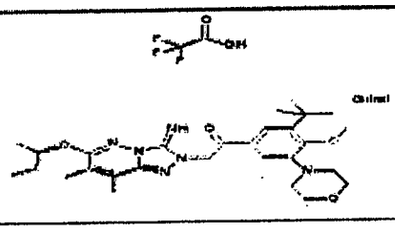
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 062		N,N-diethyl-6-chloro-3-imino-2-{2-[3-methoxy-5-(pentafluoro-sulfanyl)phenyl]-2-oxoethyl}-2,3-dihydro-[1,2,4]triazolo[4,3-b]-pyridazine-8-carboxamide trifluoroacetic acid salt	1.25	543.0 (met. a)
Ex.: 063		2-(6-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluoro-sulfanyl)phenyl]ethanone trifluoroacetic acid salt	1.18	438.0 (met. a)
Ex.: 064		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.27	459.3 (met. a)
Ex.: 065		1-[3-tert-butyl-5-(3-methoxy-propoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.52	498.5 (met. a)
Ex.: 066		1-[3-tert-butyl-5-(2-methoxy-ethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.48	484.4 (met. a)
Ex.: 067		1-(3-tert-butyl-5-cyclopropyl-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.63	480.5 (met. a)
Ex.: 068		1-(3-tert-butyl-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.52	440.4 (met. a)

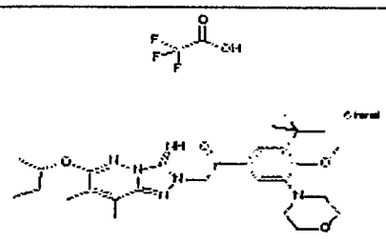
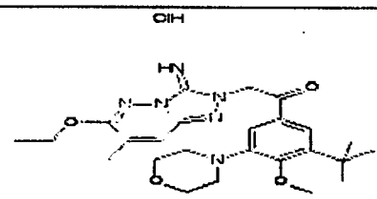
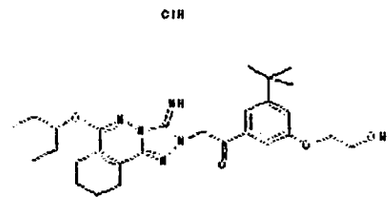
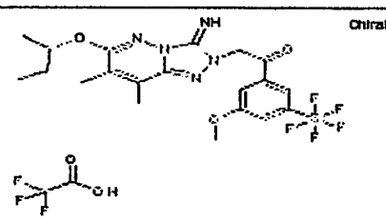
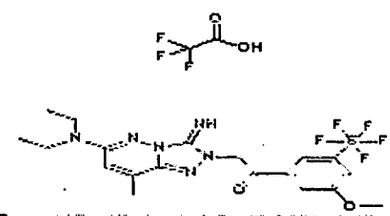
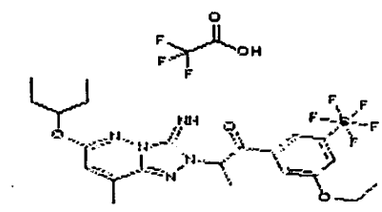
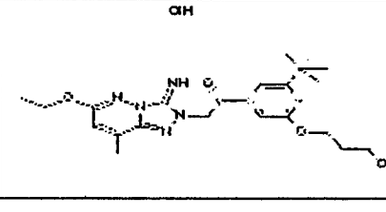
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 069		1-[3-tert-butyl-5-(3-methoxy-propoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.55	498.5 (met. a)
Ex.: 070		2-(6-chloro-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)-phenyl]ethanone trifluoroacetic acid salt	1.47	472.1 (met. a)
Ex.: 071		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.57	487.2 (met. a)
Ex.: 072		N,N-diethyl-6-chloro-3-imino-2-(2-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-2-oxoethyl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide trifluoroacetic acid salt	1.47	543.1 (met. a)
Ex.: 073		N,N-diethyl-2-[2-(3-tert-butyl-4-methoxy-5-morpholin-4-yl-phenyl)-2-oxoethyl]-6-chloro-3-imino-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide trifluoroacetic acid salt	1.55	558.3 (met. a)
Ex.: 074		1-[3-tert-butyl-5-(3-methoxypropoxy)phenyl]-2-(6-ethoxy-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.89	456.2 (met. b)
Ex.: 075		1-[3-tert-butyl-5-(2-methoxyethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.48	484.5 (met. a)

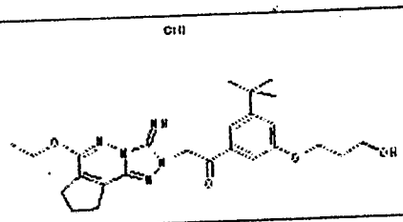
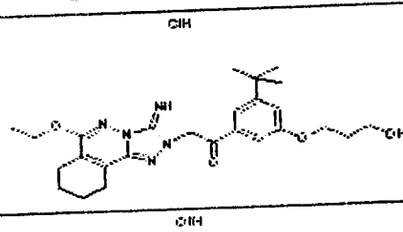
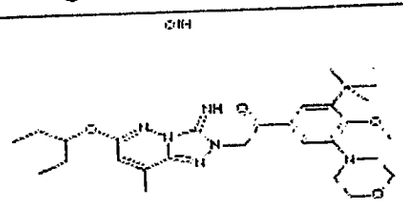
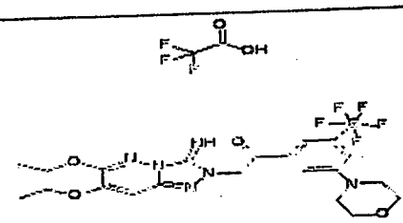
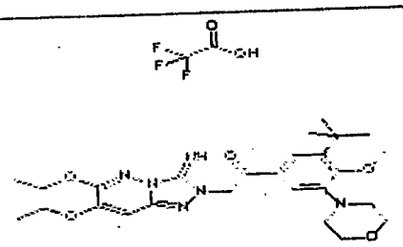
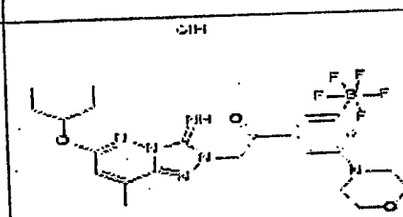
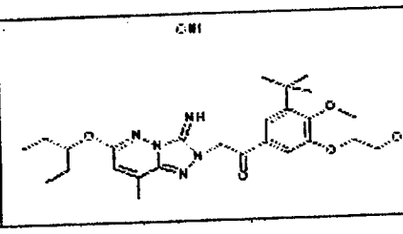
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 076		1-(3-tert-butyl-5-methoxy-phenyl)-2-[6-(1-ethylpropoxy)-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	0.83	472.2 (met. b)
Ex.: 077		1-[3-tert-butyl-5-(3-hydroxy-propoxymethyl)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone hydrochloride	1.38	498.2 (met. a)
Ex.: 078		N,N-diethyl- 6-ethoxy-3-imino-2-[2-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-2-oxoethyl]-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide trifluoroacetic acid salt	1.26	553.2 (met. a)
Ex.: 079		2-(3-imino-6-methoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)-phenyl]ethanone trifluoroacetic acid salt	1.24	468.1 (met. a)
Ex.: 080		2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluoros ulfanyl)-phenyl]ethanone trifluoroacetic acid salt	1.32	482.1 (met. a)
Ex.: 081		1-(3-tert-butyl-4-methoxy-5-morpholin-4-yl-phenyl)-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.38	497.2 (met. a)
Ex.: 082		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-7-diethylamino-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.40	530.2 (met. a)

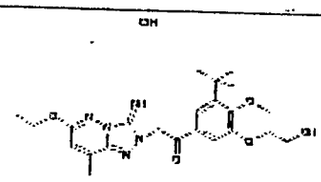
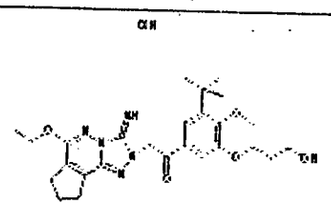
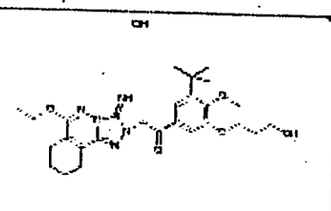
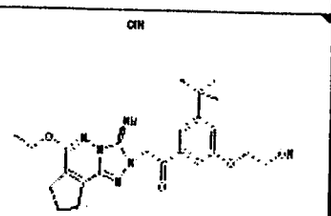
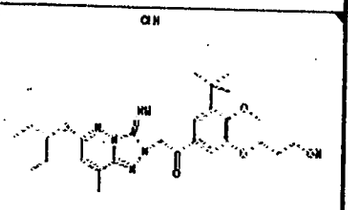
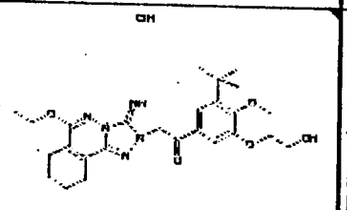
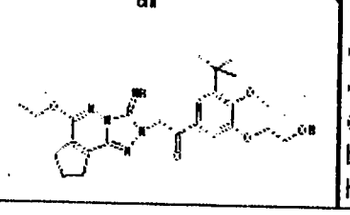
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 083		2-(6-chloro-7-diethylamino-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)-phenyl]ethanone trifluoroacetic acid salt	1.32	515.1 (met. a)
Ex.: 084		2-(7-diethylamino-6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)-phenyl]ethanone trifluoroacetic acid salt	1.65	525.2 (met. a)
Ex.: 085		2-[6-(1-ethylpropoxy)-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methoxy-5-(pentafluorosulfanyl)-phenyl]ethanone trifluoroacetic acid salt	1.47	524.2 (met. a)
Ex.: 086		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.52	539.3 (met. a)
Ex.: 087		N,N-diethyl-2-[2-(3-tert-butyl-4-methoxy-5-morpholin-4-yl-phenyl)-2-oxoethyl]-6-ethoxy-3-imino-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide trifluoroacetic acid salt	1.32	568.3 (met. a)
Ex.: 088		N,N-diethyl-2-[2-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-oxoethyl]-6-ethoxy-3-imino-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxamide trifluoroacetic acid salt	1.35	568.2 (met. a)
Ex.: 089		1-[3-tert-butyl-5-(2-hydroxyethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.35	470.2 (met. a)

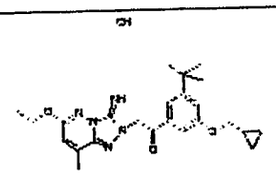
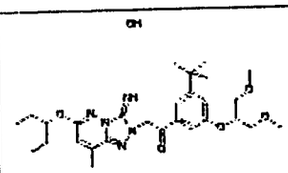
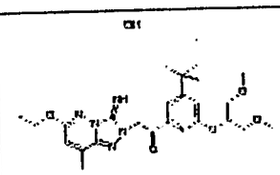
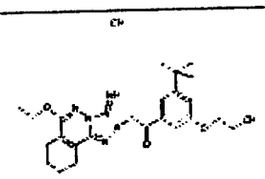
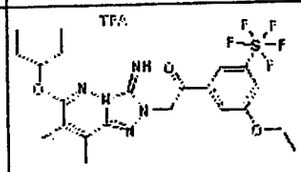
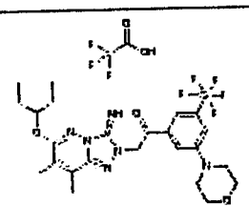
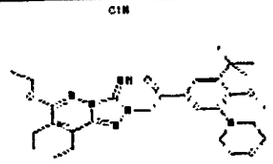
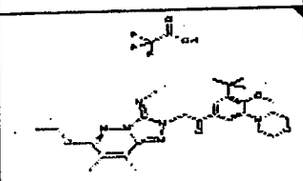
		Name	LCMS-rt [min]	[M+H]+
Ex.: 090		1-[3-tert-butyl-5-(3-hydroxy-propoxy)phenyl]-2-[6-(1-ethyl-propoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.38	484.2 (met. a)
Ex.: 091		1-[3-tert-butyl-5-(3-methoxy-propoxy)phenyl]-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.34	466.2 (met. a)
Ex.: 092		1-[3-ethoxy-5-(pentafluoro-sulfanyl)phenyl]-2-[6-(1-ethyl-propoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.47	524.2 (met. a)
Ex.: 093		N,N-diethyl-6-ethoxy-3-imino-2-(2-[3-methoxy-5-(pentafluoro-sulfanyl)phenyl]-2-oxoethyl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxamide trifluoroacetic acid salt	1.28	553.2 (met. a)
Ex.: 094		2-(3-imino-8-methyl-6-pyrrolidin-1-yl-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluoro-sulfanyl)phenyl]ethanone trifluoroacetic acid salt	1.27	493.1 (met. a)
Ex.: 095		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-8-methyl-6-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.36	508.3 (met. a)
Ex.: 096		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.16	428.3 (met. a)

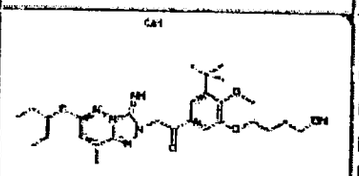
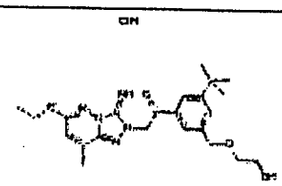
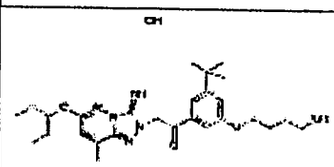
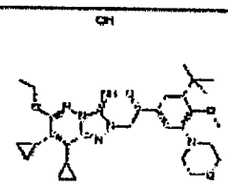
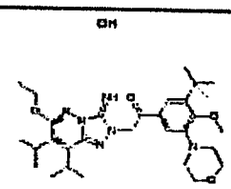
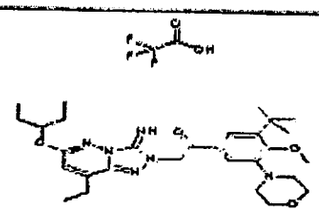
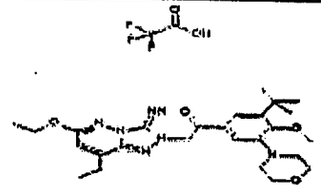
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 097		1-[3-tert-butyl-5-(2-hydroxy-ethoxymethyl)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.34	484.2 (met. a)
Ex.: 098		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-[3-imino-6-(2-methoxy-1-methoxymethyl-ethoxy)-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.15	502.2 (met. a)
Ex.: 099		1-[3-tert-butyl-5-(3-hydroxy-propoxy)phenyl]-2-[3-imino-6-(2-methoxy-1-methoxymethyl-ethoxy)-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.21	516.3 (met. a)
Ex.: 100		1-[3-tert-butyl-5-(3-hydroxy-propoxy)phenyl]-2-[6-(1-ethyl-propoxy)-3-imino-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazin-2-yl]ethanone hydrochloride	0.99	524.3 (met. b)
Ex.: 101		1-[3-tert-butyl-5-(3-methoxy-propoxy)phenyl]-2-[6-(2-hydroxyethoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.24	472.2 (met. a)
Ex.: 102		2-[6-((R)-sec-butoxy)-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-trifluoroacetic acid salt	1.05	510.2 (met. b)
Ex.: 103		2-[6-((R)-sec-butoxy)-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-(3-tert-butyl-4-methoxy-5-morpholin-4-yl-phenyl)ethanone trifluoroacetic acid salt	1.06	525.4 (met. b)

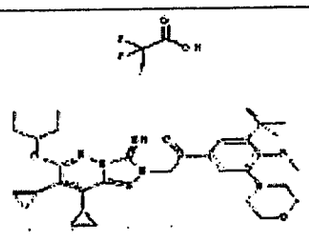
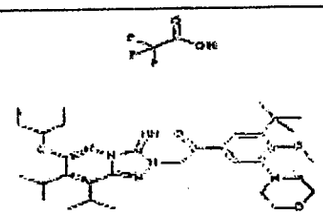
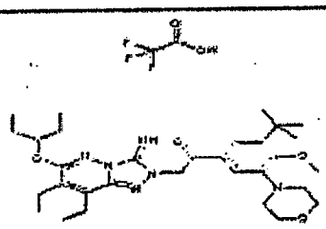
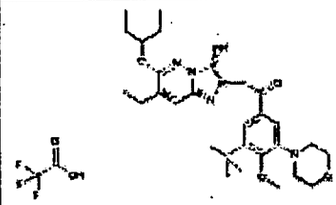
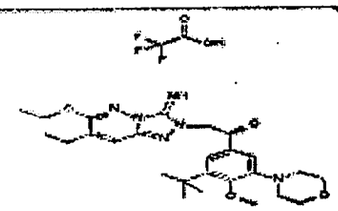
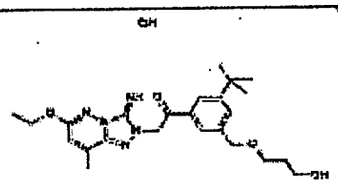
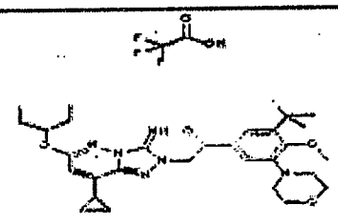
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 104		2-[6-((S)-sec-butoxy)-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-(3-tert-butyl-4-methoxy-5-morpholin-4-yl-phenyl)ethanone trifluoroacetic acid salt	1.08	525.4 (met. b)
Ex.: 105		1-(3-tert-butyl-4-methoxy-5-morpholin-4-yl-phenyl)-2-(6-ethoxy-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.38	483.3 (met. a)
Ex.: 106		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)-phenyl]-2-[6-(1-ethyl-propoxy)-3-imino-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazin-2-yl]ethanone hydrochloride	1.48	510.3 (met. a)
Ex.: 107		2-[6-((S)-sec-butoxy)-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-ethanone hydrochloride	1.05	510.2 (met. b)
Ex.: 108		2-(6-diethylamino-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-ethanone trifluoroacetic acid salt	1.01	495.2 (met. b)
Ex.: 109		1-[3-ethoxy-5-(pentafluoro-sulfanyl)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]propan-1-one trifluoroacetic acid salt	1.07	538.2 (met. b)
Ex.: 110		1-[3-tert-butyl-5-(3-hydroxy-propoxy)phenyl]-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.33	442.3 (met. a)

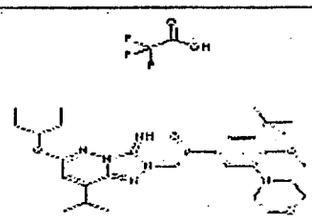
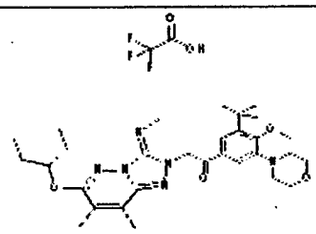
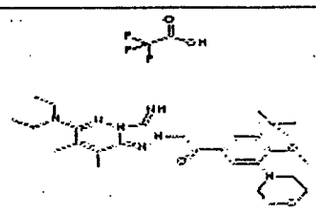
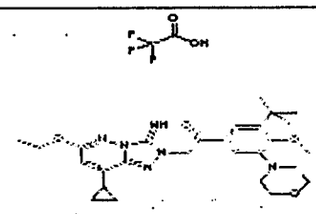
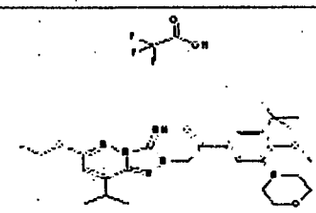
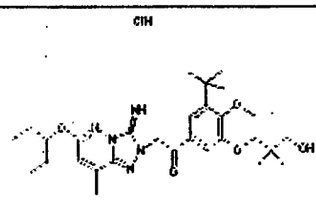
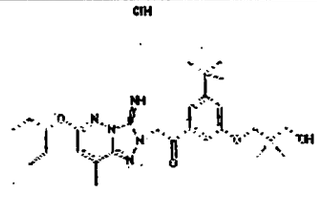
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 111		1-[3-tert-butyl-5-(3-hydroxy-propoxy)phenyl]-2-(6-ethoxy-3-imino-6,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.3	468.2 (met. a)
Ex.: 112		1-[3-tert-butyl-5-(3-hydroxy-propoxy)phenyl]-2-(6-ethoxy-3-imino-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazin-2-yl)ethanone hydrochloride	1.36	482.2 (met. a)
Ex.: 113		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone hydrochloride	1.53	525.3 (met. a)
Ex.: 114		2-(6,7-diethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-morpholin-4-yl-5-(pentafluorosulfanyl)phenyl]-ethanone trifluoroacetic acid salt	0.91	553.2 (met. b)
Ex.: 115		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6,7-diethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.01	513.4 (met. b)
Ex.: 116		2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-morpholin-4-yl-5-(pentafluoro-sulfanyl)phenyl]ethanone hydrochloride	1.05	565.3 (met. b)
Ex.: 117		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)-4-methoxyphenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone hydrochloride	1.38	500.3 (met. a)

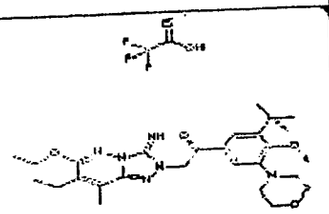
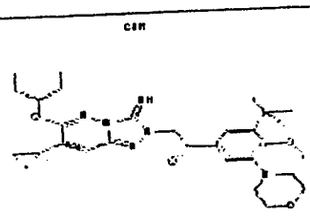
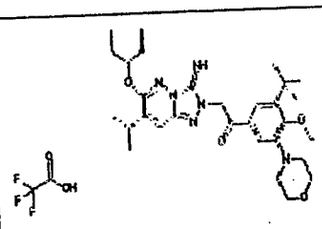
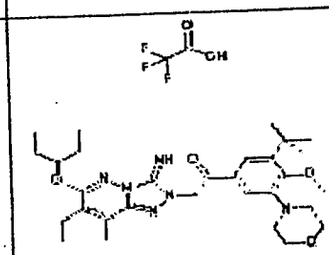
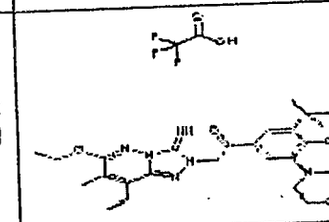
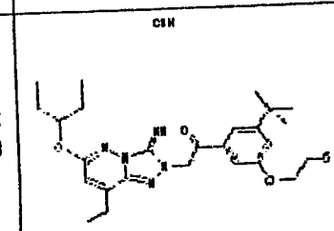
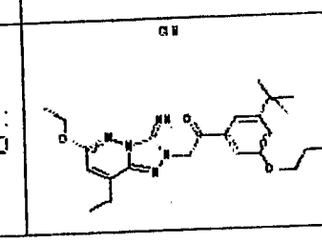
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 118		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.19	458.3 (met. a)
Ex.: 119		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-8,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo [4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.32	498.2 (met. a)
Ex.: 120		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazin-2-yl)ethanone hydrochloride	1.38	512.3 (met. a)
Ex.: 121		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-3-imino-8,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.24	454.2 (met. a)
Ex.: 122		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.41	514.2 (met. a)
Ex.: 123		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]-phthalazin-2-yl)ethanone hydrochloride	1.27	498.2 (met. a)
Ex.: 124		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-8,9-dihydro-7H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.21	484.2 (met. a)

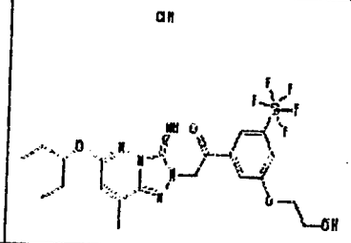
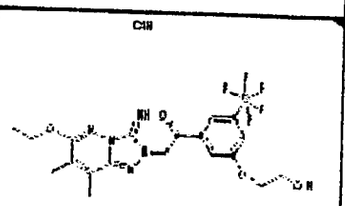
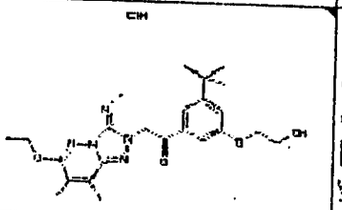
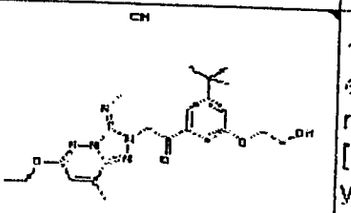
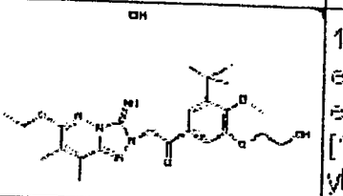
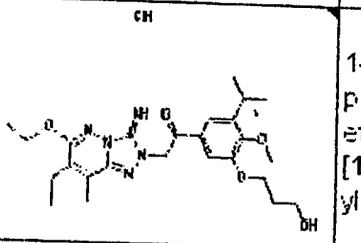
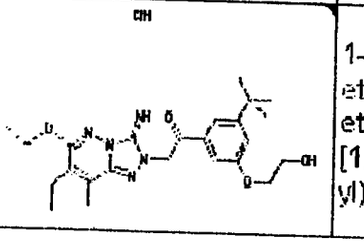
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 125		1-(3-tert-butyl-5-cyclopropyl-methoxyphenyl)-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.4	438.3 (met. a)
Ex.: 126		1-[3-tert-butyl-5-(2-methoxy-1-methoxymethylethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone hydrochloride	1.46	528.3 (met. a)
Ex.: 127		1-[3-tert-butyl-5-(2-methoxy-1-methoxymethylethoxy)phenyl]-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.31	486.2 (met. a)
Ex.: 128		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-3-imino-7,8,9,10-tetrahydro-[1,2,4]triazolo[3,4-a]phthalazin-2-yl)ethanone hydrochloride	1.3	468.2 (met. a)
Ex.: 129		1-[3-ethoxy-5-(pentafluoro-sulfanyl)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.1	538.2 (met. b)
Ex.: 130		2-[6-(1-ethylpropoxy)-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-morpholin-4-yl-5-(pentafluoro-sulfanyl)-phenyl]ethanone trifluoroacetic acid salt	1.05	565.3 (met. b)
Ex.: 131		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-7,8-diethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.09	525.4 (met. b)
Ex.: 132		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-ethoxy-7,8-dimethyl-3-[(E)-methylimino]-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.08	511.4 (met. b)

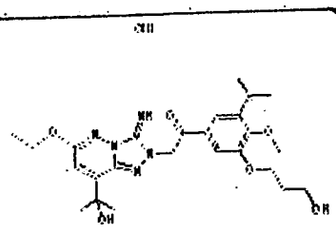
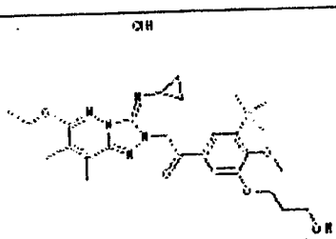
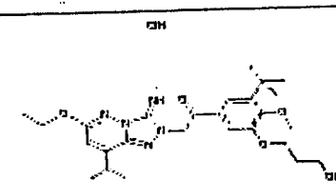
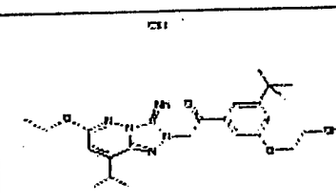
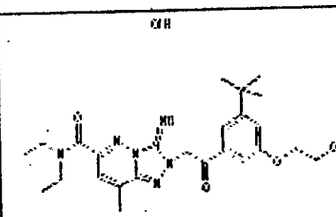
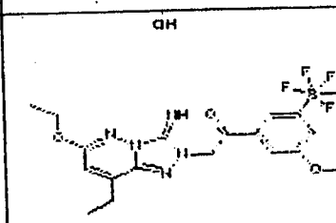
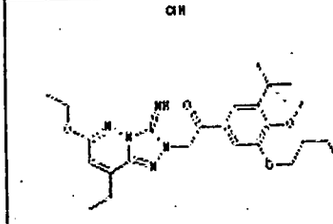
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 133		1-[3-tert-butyl-5-(4-hydroxy-butoxy)-4-methoxyphenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.42	528.3 (met. a)
Ex.: 134		1-[3-tert-butyl-5-(2-hydroxy-ethoxymethyl)phenyl]-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.16	442.3 (met. a)
Ex.: 135		1-[3-tert-butyl-5-(4-hydroxy-butoxy)phenyl]-2-[6-(1-ethyl-propoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.4	498.2 (met. a)
Ex.: 136		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(7,8-dicyclopropyl-6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.11	549.4 (met. b)
Ex.: 137		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-3-imino-7,8-diisopropyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.15	553.4 (met. b)
Ex.: 138		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[8-ethyl-6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.11	539.4 (met. b)
Ex.: 139		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-8-ethyl-3-imino-[1,2,4]-triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.04	497.3 (met. b)

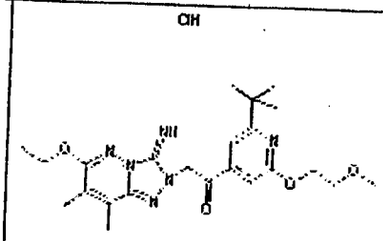
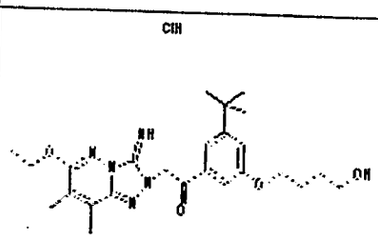
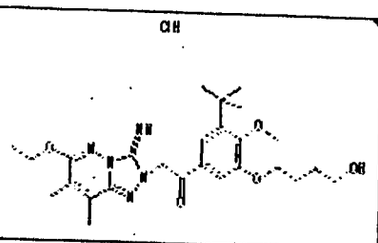
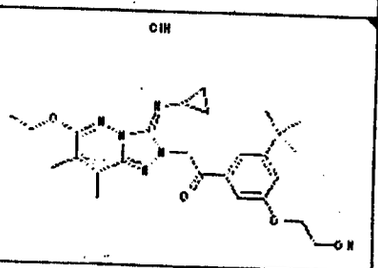
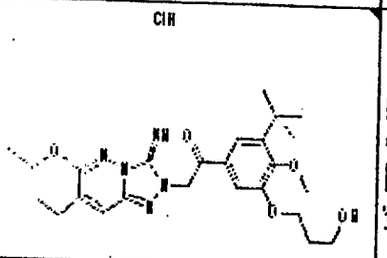
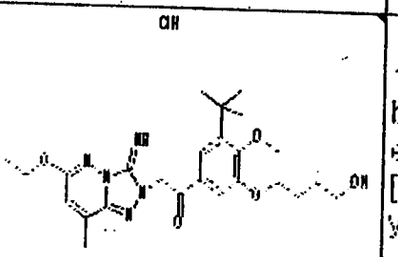
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 140		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[7,8-dicyclopropyl-6-(1-ethyl-propoxy)-3-imino-[1,2,4]-triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.16	591.4 (met. b)
Ex.: 141		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-7,8-diisopropyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.19	595.5 (met. b)
Ex.: 142		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[7,8-diethyl-6-(1-ethyl-propoxy)-3-imino-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.15	567.4 (met. b)
Ex.: 143		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[7-ethyl-6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.11	539.4 (met. b)
Ex.: 144		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-7-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.04	497.3 (met. b)
Ex.: 145		1-[3-tert-butyl-5-(3-hydroxy-propoxymethyl)phenyl]-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.19	459.2 (met. a)
Ex.: 146		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[8-cyclopropyl-6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.11	551.4 (met. b)

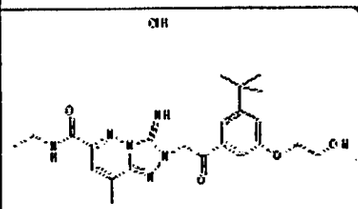
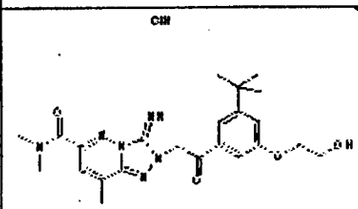
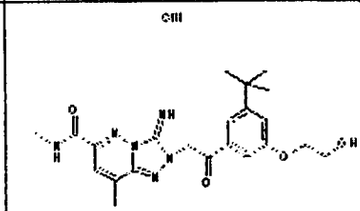
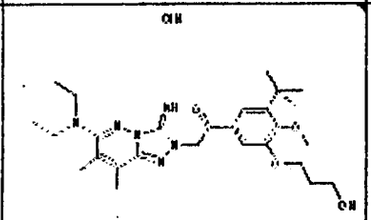
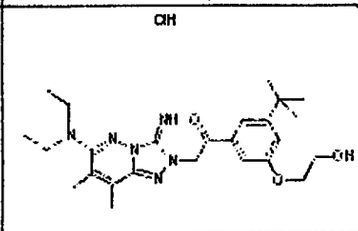
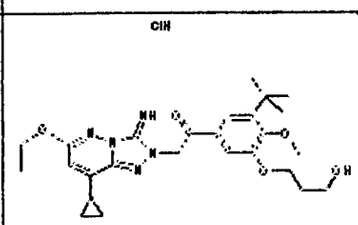
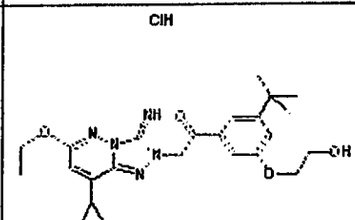
		Name	LCMS-rt [min]	$[M+H^+]^+$
Ex.: 147		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-8-isopropyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.13	553.4 (met. b)
Ex.: 148		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-(1-ethylpropoxy)-7,8-dimethyl-3-[(E)-methylimino]-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.12	553.4 (met. b)
Ex.: 149		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-diethylamino-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.08	524.4 (met. b)
Ex.: 150		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclopropyl-8-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.05	509.3 (met. b)
Ex.: 151		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-3-imino-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.07	511.4 (met. b)
Ex.: 152		1-[3-tert-butyl-5-(3-hydroxy-2,2-dimethylpropoxy)-4-methoxy-phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.5	542.3 (met. a)
Ex.: 153		1-[3-tert-butyl-5-(3-hydroxy-2,2-dimethylpropoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.48	512.3 (met. a)

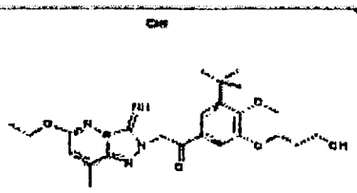
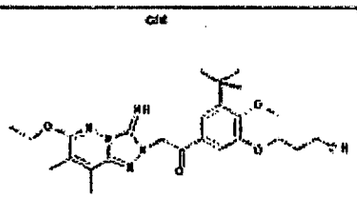
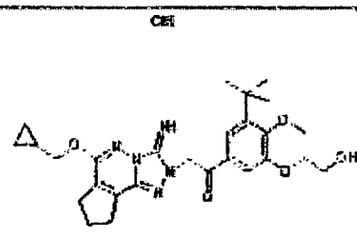
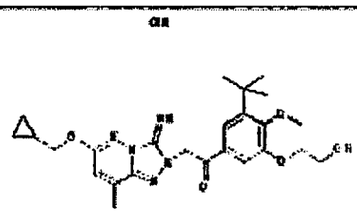
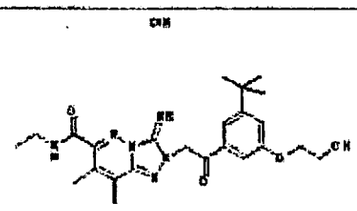
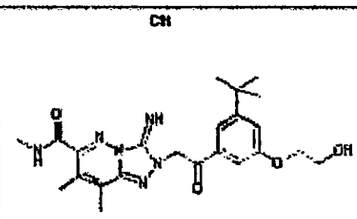
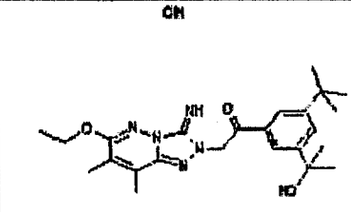
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 154		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-7-ethyl-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.07	511.4 (met. b)
Ex.: 155		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[7-cyclopropyl-6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.12	551.4 (met. b)
Ex.: 156		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-7-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.13	553.4 (met. b)
Ex.: 157		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[7-ethyl-6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone trifluoroacetic acid salt	1.14	553.4 (met. b)
Ex.: 158		1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-8-ethyl-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone trifluoroacetic acid salt	1.07	511.4 (met. b)
Ex.: 159		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-[8-ethyl-6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.03	484.4 (met. b)
Ex.: 160		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-8-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.95	442.3 (met. b)

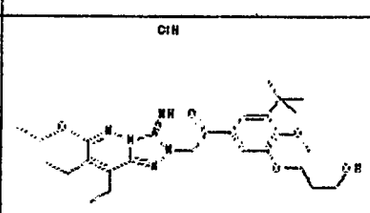
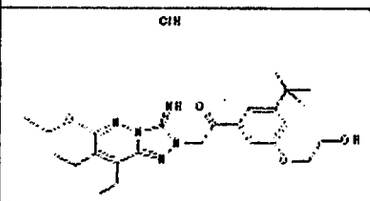
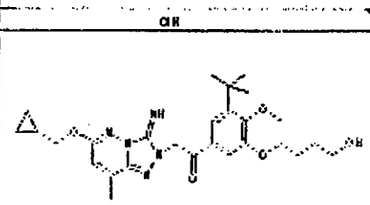
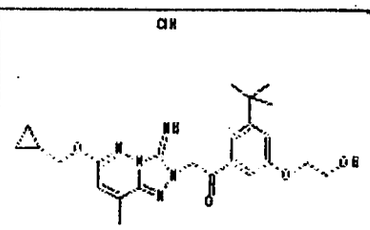
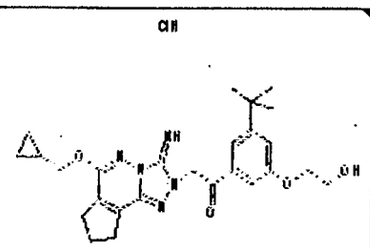
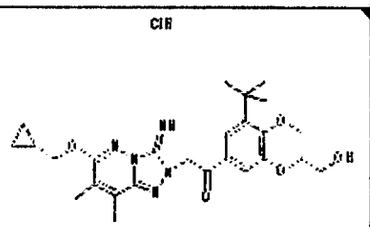
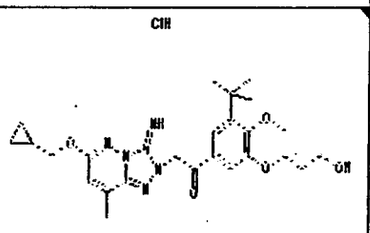
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 161		2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-(2-hydroxy-ethoxy)-5-(pentafluoro-sulfanyl)-phenyl]ethanone trifluoroacetic acid salt	0.89	540.2 (met. b)
Ex.: 162		2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-(2-hydroxy-ethoxy)-5-(pentafluoro-sulfanyl)-phenyl]ethanone hydrochloride	1.23	512.2 (met. a)
Ex.: 163		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-[6-ethoxy-7,8-dimethyl-3-[(E)-methylimino]-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	0.97	456.3 (met. b)
Ex.: 164		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-8-methyl-3-[(E)-methylimino]-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.94	442.3 (met. b)
Ex.: 165		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.83	472.2 (met. b)
Ex.: 166		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-7-ethyl-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.03	500.3 (met. b)
Ex.: 167		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-7-ethyl-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.98	456.3 (met. b)

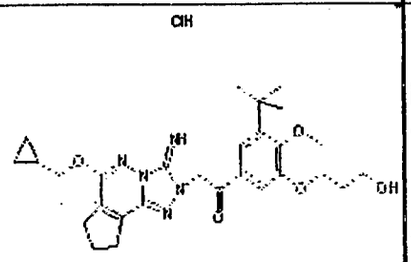
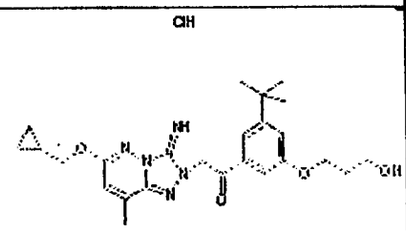
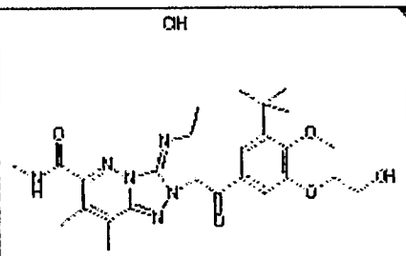
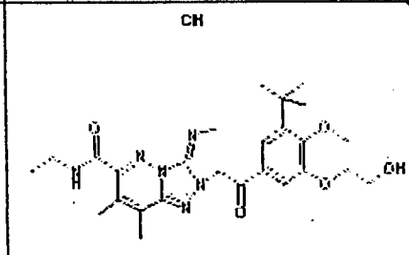
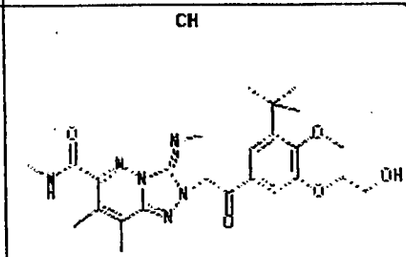
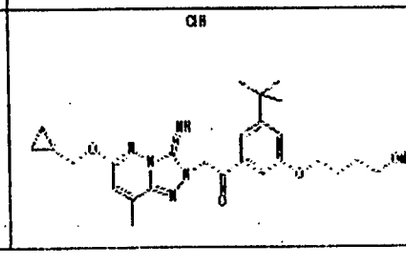
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 168		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-[6-ethoxy-8-(1-hydroxy-1-methyl-ethyl)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	0.96	516.3 (met. b)
Ex.: 169		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(3-[(E)-cyclopropylimino]-6-ethoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.04	526.4 (met. b)
Ex.: 170		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.03	500.3 (met. b)
Ex.: 171		1-[3-tert-butyl-5-(2-hydroxy-ethoxy) phenyl]-2-(6-ethoxy-3-imino-8-isopropyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.00	456.3 (met. b)
Ex.: 172		N,N-diethyl-2-(2-[3-tert-butyl-5-(2-hydroxyethoxy)phenyl]-2-oxoethyl)-3-imino-8-methyl-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.74	483.3 (met. b)
Ex.: 173		2-(6-ethoxy-8-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-ethanone hydrochloride	1.02	482.2 (met. b)
Ex.: 174		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-8-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.00	486.3 (met. b)

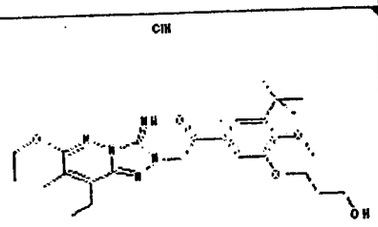
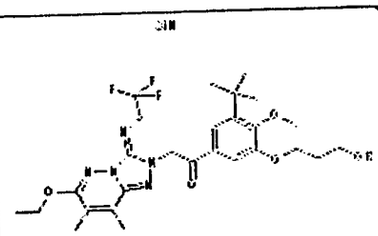
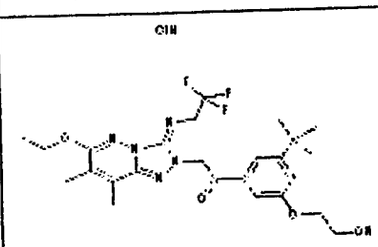
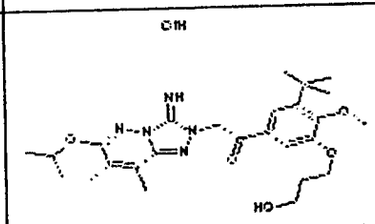
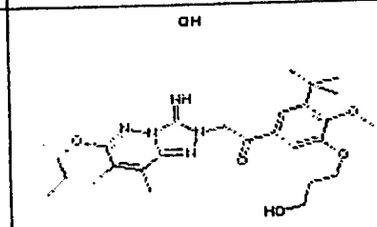
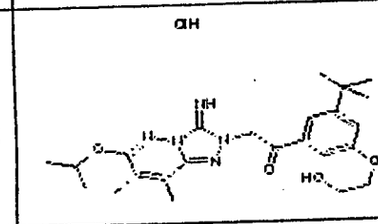
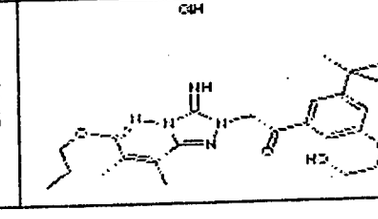
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 175		1-[2-tert-butyl-6-(2-methoxy-ethoxy)pyridin-4-yl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.83	472.2 (met. b)
Ex.: 176		1-[3-tert-butyl-5-(4-hydroxy-butoxy)phenyl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.82	470.2 (met. b)
Ex.: 178		1-[3-tert-butyl-5-(4-hydroxy-butoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.86	500.3 (met. b)
Ex.: 179		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-[3-[(E)-cyclopropylimino]-6-ethoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	0.99	482.3 (met. b)
Ex.: 180		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-7-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.99	486.3 (met. b)
Ex.: 181		1-[3-tert-butyl-5-(4-hydroxy-butoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.86	482.2 (met. b)

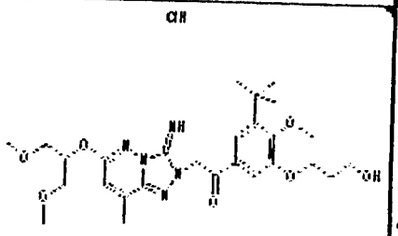
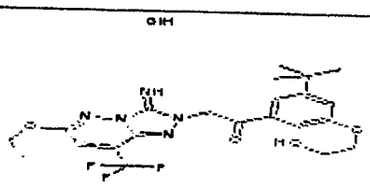
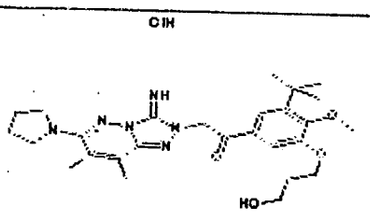
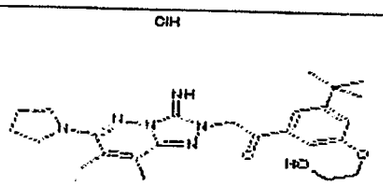
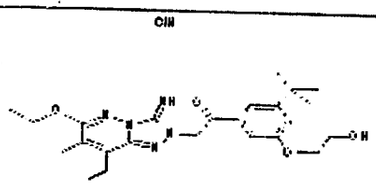
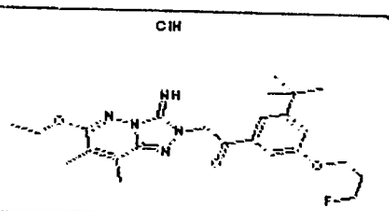
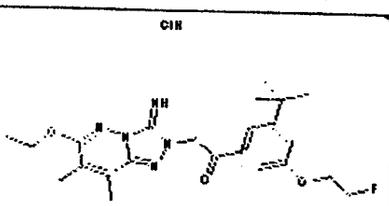
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 182		N-ethyl- 2-{2-[3-tert-butyl-5-(2-hydroxyethoxy)phenyl]-2-oxo-ethyl}-3-imino-8-methyl-2,3-dihydro-[1,2,4]triazolo[4,3-b]-pyridazine-6-carboxamide hydrochloride	0.74	456.2 (met. b)
Ex.: 183		N,N-dimethyl- 2-{2-[3-tert-butyl-5-(2-hydroxyethoxy)phenyl]-2-oxo-ethyl}-3-imino-8-methyl-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.7	455.3 (met. b)
Ex.: 184		N-methyl- 2-{2-[3-tert-butyl-5-(2-hydroxyethoxy)phenyl]-2-oxo-ethyl}-3-imino-8-methyl-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.7	441.2 (met. b)
Ex.: 186		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-diethylamino-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.02	513.4 (met. b)
Ex.: 187		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-diethylamino-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.98	469.4 (met. b)
Ex.: 188		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-cyclopropyl-8-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.00	496.3 (met. b)
Ex.: 189		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-cyclopropyl-8-ethoxy-3-imino-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.98	454.3 (met. b)

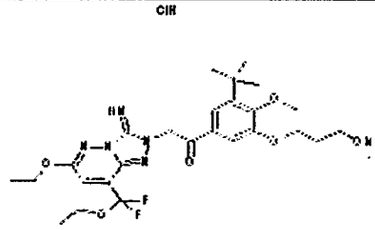
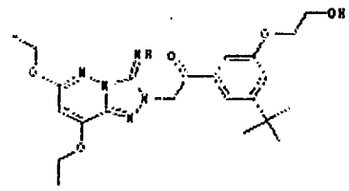
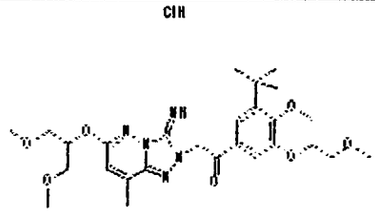
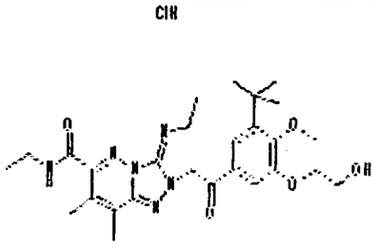
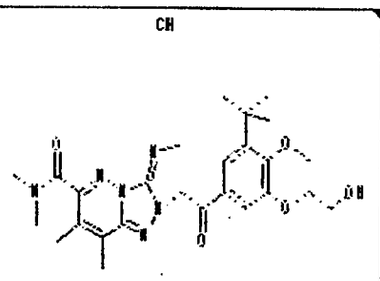
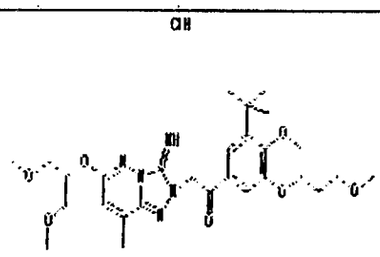
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 190		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.82	472.2 (met. b)
Ex.: 191		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.85	486.2 (met. b)
Ex.: 192		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)-4-methoxyphenyl]-2-(6-cyclopropylmethoxy-3-imino-8,9-dihydro-7H-cyclopenta[d]-[1,2,4]triazolo [4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.89	510.2 (met. b)
Ex.: 193		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)-4-methoxyphenyl]-2-(6-cyclopropylmethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl)ethanone hydrochloride	0.83	484.2 (met. b)
Ex.: 194		N-ethyl- 2-{2-[3-tert-butyl-5-(2-hydroxyethoxy)phenyl]-2-oxo-ethyl}-3-imino-7,8-dimethyl-2,3-dihydro-[1,2,4]triazolo[4,3-b]-pyridazine-6-carboxamide hydrochloride	0.73	469.2 (met. b)
Ex.: 195		N-methyl- 2-{2-[3-tert-butyl-5-(2-hydroxyethoxy)phenyl]-2-oxo-ethyl}-3-imino-7,8-dimethyl-2,3-dihydro-[1,2,4]triazolo-[4,3-b]-pyridazine-6-carboxamide hydrochloride	0.71	455.3 (met. b)
Ex.: 196		1-[3-tert-butyl-5-(1-hydroxy-1-methyl ethyl) phenyl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.98	440.3 (met. b)

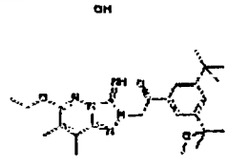
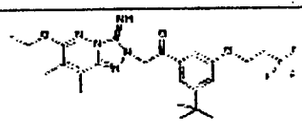
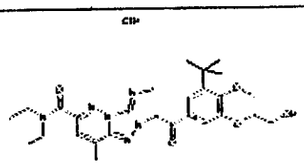
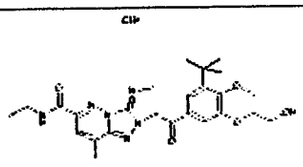
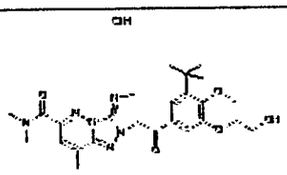
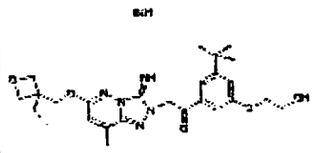
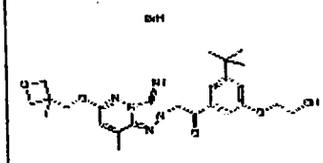
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 197		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-7,8-diethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.06	514.4 (met. b)
Ex.: 198		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-7,8-diethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.02	470.3 (met. b)
Ex.: 199		1-[3-tert-butyl-5-(4-hydroxy-butoxy)-4-methoxyphenyl]-2-(6-cyclopropylmethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.87	512.3 (met. b)
Ex.: 200		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-cyclopropylmethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.81	454.2 (met. b)
Ex.: 201		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-cyclopropylmethoxy-3-imino-8,9-dihydro-7H-cyclopenta[d]-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.85	480.2 (met. b)
Ex.: 202		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)-4-methoxyphenyl]-2-(6-cyclopropylmethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.87	498.2 (met. b)
Ex.: 203		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-cyclopropylmethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl)ethanone hydrochloride	0.86	498.2 (met. b)

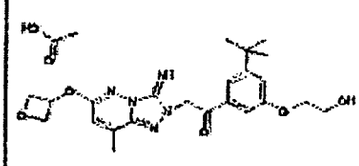
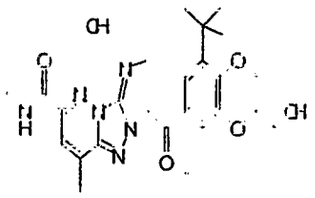
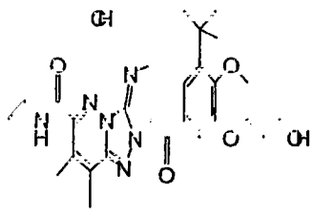
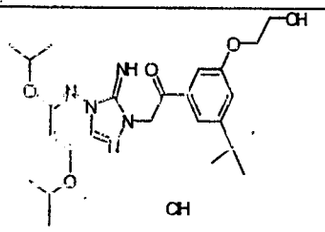
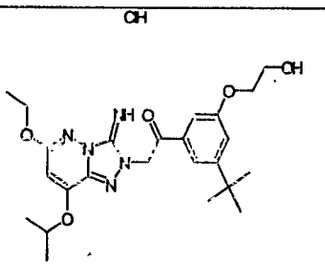
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 204		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-cyclopropylmethoxy-3-imino-8,9-dihydro-7H-cyclopenta[d]-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.88	524.3 (met. b)
Ex.: 205		1-[3-tert-butyl-5-(3-hydroxy-propoxy)phenyl]-2-(6-cyclopropylmethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.83	468.2 (met. b)
Ex.: 206		N-methyl- 2-(2-[3-tert-butyl-5-(2-hydroxyethoxy)-4-methoxy-phenyl]-2-oxoethyl)-3-[(E)-ethylimino]-7,8-dimethyl-2,3-dihydro-[1,2,4]triazolo[4,3-b]-pyridazine-6-carboxamide hydrochloride	0.76	513.3 (met. b)
Ex.: 207		N-ethyl- 2-(2-[3-tert-butyl-5-(2-hydroxyethoxy)-4-methoxy-phenyl]-2-oxoethyl)-7,8-dimethyl-3-[(E)-methylimino]-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.77	513.3 (met. b)
Ex.: 208		N-methyl- 2-(2-[3-tert-butyl-5-(2-hydroxyethoxy)-4-methoxy-phenyl]-2-oxoethyl)-7,8-dimethyl-3-[(E)-methylimino]-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.75	499.2 (met. b)
Ex.: 209		1-[3-tert-butyl-5-(4-hydroxy-butoxy)phenyl]-2-(6-cyclopropylmethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.85	482.2 (met. b)

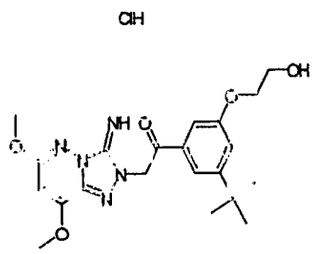
		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 210		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(6-ethoxy-8-ethyl-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.02	500.4 (met. b)
Ex.: 211		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-[6-ethoxy-7,8-dimethyl-3-[(E)-2,2,2-trifluoroethylimino]-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.04	568.3 (met. b)
Ex.: 212		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-[6-ethoxy-7,8-dimethyl-3-[(E)-2,2,2-trifluoroethylimino]-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.01	524.3 (met. b)
Ex.: 213		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-[6-ethoxy-7,8-dimethyl-3-[(E)-2,2,2-trifluoro-ethylimino]-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.02	500.4 (met. b)
Ex.: 214		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(3-imino-7,8-dimethyl-6-propoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.02	500.3 (met. b)
Ex.: 215		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(3-imino-6-isopropoxy-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.98	456.3 (met. b)
Ex.: 216		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(3-imino-7,8-dimethyl-6-propoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.98	456.3 (met. b)

		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 217		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-[3-imino-6-(2-methoxy-1-methoxy-methylethoxy)-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	0.8	546.3 (met. b)
Ex.: 218		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-3-imino-8-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.97	482.3 (met. b)
Ex.: 219		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-(3-imino-7,8-dimethyl-6-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl)ethanone hydrochloride	1.01	511.4 (met. b)
Ex.: 220		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(3-imino-7,8-dimethyl-6-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.97	467.3 (met. b)
Ex.: 221		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-8-ethyl-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.97	456.3 (met. b)
Ex.: 222		1-[3-tert-butyl-5-(3-fluoro-propoxy)phenyl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.04	458.3 (met. b)
Ex.: 223		1-[3-tert-butyl-5-(2-fluoro-ethoxy)phenyl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	1.02	444.3 (met. b)

		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 224		1-[3-tert-butyl-5-(3-hydroxy-propoxy)-4-methoxyphenyl]-2-[6-ethoxy-8-(ethoxydifluoromethyl)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	1.02	552.3 (met. b)
Ex.: 225		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6,8-diethoxy-3-imino-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl)ethanone hydrochloride	0.82	458.2 (met. b)
Ex.: 226		1-[3-tert-butyl-4-methoxy-5-(2-methoxyethoxy)phenyl]-2-[3-imino-6-(2-methoxy-1-methoxymethylethoxy)-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	0.85	546.3 (met. b)
Ex.: 227		N-ethyl- 2-(2-[3-tert-butyl-5-(2-hydroxyethoxy)-4-methoxy-phenyl]-2-oxoethyl)-3-[(E)-ethylimino]-7,8-dimethyl-2,3-dihydro-[1,2,4]triazolo[4,3-b]-pyridazine-6-carboxamide hydrochloride	0.78	527.2 (met. b)
Ex.: 228		N,N-dimethyl- 2-(2-[3-tert-butyl-5-(2-hydroxyethoxy)-4-methoxy-phenyl]-2-oxoethyl)-7,8-dimethyl-3-[(E)-methylimino]-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.75	513.3 (met. b)
Ex.: 229		1-[3-tert-butyl-4-methoxy-5-(3-methoxypropoxy)phenyl]-2-[3-imino-6-(2-methoxy-1-methoxymethylethoxy)-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone hydrochloride	0.88	560.3 (met. b)

		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 230		1-[3-tert-butyl-5-(1-methoxy-1-methylethyl)phenyl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.99	454.3 (met. b)
Ex.: 231		1-[3-tert-butyl-5-(3,3,3-trifluoro-propoxy)phenyl]-2-(6-ethoxy-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.98	494.2 (met. b)
Ex.: 232		N,N-diethyl-2-[2-[3-tert-butyl-5-(2-hydroxyethoxy)-4-methoxy-phenyl]-2-oxo-ethyl]-8-methyl-3-[(E)-methylimino]-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.78	527.2 (met. b)
Ex.: 233		N-ethyl-2-[2-[3-tert-butyl-5-(2-hydroxyethoxy)-4-methoxy-phenyl]-2-oxo-ethyl]-8-methyl-3-[(E)-methylimino]-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.77	499.2 (met. b)
Ex.: 234		N,N-dimethyl-2-[2-[3-tert-butyl-5-(2-hydroxyethoxy)-4-methoxy-phenyl]-2-oxo-ethyl]-8-methyl-3-[(E)-methylimino]-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.74	499.2 (met. b)
Ex.: 235		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-[6-(3-ethyl-oxetan-3-ylmethoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone hydrobromide	0.76	498.2 (met. b)
Ex.: 236		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-[3-imino-8-methyl-6-(3-methyloxetan-3-ylmethoxy)-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl]ethanone hydrobromide	0.75	484.2 (met. b)

		Name	LCMS-rt [min]	$[M+H]^+$
Ex.: 237		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-[3-imino-8-methyl-6-(oxetan-3-yloxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone	0.73	456.2 (met. b)
Ex.: 238		N-methyl-2-{2-[3-tert-butyl-5-(2-hydroxyethoxy)-4-methoxy-phenyl]-2-oxoethyl}-8-methyl-3-[(E)-methylimino]-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.76	485.2 (met. b)
Ex.: 239		N-ethyl-2-{2-[3-tert-butyl-5-(3-hydroxypropoxy)-4-methoxy-phenyl]-2-oxoethyl}-7,8-dimethyl-3-[(E)-methylimino]-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide hydrochloride	0.80	527.2 (met. b)
Ex.: 240		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(3-imino-6,8-diisopropoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.90	486.3 (met. b)
Ex.: 241		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(6-ethoxy-3-imino-8-isopropoxy-[1,2,4]-triazolo[4,3-b]pyridazin-2-yl)-ethanone hydrochloride	0.86	472.2 (met. b)

Ex.: 242		1-[3-tert-butyl-5-(2-hydroxy-ethoxy)phenyl]-2-(3-imino-6,8-dimethoxy-[1,2,4]triazolo-[4,3-b]pyridazin-2-yl)ethanone hydrochloride	0.76	430.2 (met. b)

Pharmacological examples

PAR1 determination method: inhibition of PAR1-mediated platelet aggregation

The pharmacological testing of the substances took place in platelet aggregation induced by TRAP (thrombin receptor-activating peptide) in 96-well format. For this purpose, blood was taken from healthy volunteer donors in 20 ml syringes containing 2 ml of 3.13% sodium citrate solution. After centrifugation at 150 x g for 20 minutes, the platelet-rich plasma (PRP) was separated off and mixed with 1 µl of PGE1 solution (500 µg/ml in ethanol) / ml of PRP. Incubation at RT for 5 minutes was followed by centrifugation at 120 x g for 15 minutes to remove the leukocytes. The leukocyte-free PRP was transferred in 5 ml portions into 15 ml PP tubes and centrifuged at 360 x g for 15 minutes in order to pellet the platelets. The plasma was then decanted off and the platelet sediment from 5 ml of PRP was resuspended in 1 ml of Tyrode's (120 mM NaCl, 2.6 mM KCl, 12 mM $NaHCO_3$, 0.39 mM NaH_2PO_4 x H_2O, 10 mM HEPES, 0.35% BSA, 5.5 mM glucose, pH 7.4) and adjusted with Tyrode's to a platelet count of 3 x 10^5 / microliter (µL). 13 ml of this cell suspension were then mixed with 866 µL of 10 mM $CaCl_2$ solution, and 120 µL thereof were pipetted into each well of a 96-well plate containing 15 µL of the substance to be tested. After incubation at room temperature in the dark for 30 minutes, 15 µL of a TRAP solution (70-100 µM) were added as agonist, and kinetics were recorded at 650 nm in a SpectraMax 340 at 37°C for 20 minutes while shaking. The areas under the curves of negative control (Tyrode's/ DMSO) and positive control (15 µl of agonist /DMSO) were calculated and the difference was fixed as the 100% value. The substances to be tested were pipetted as serial dilutions in duplicate determination, the AUC was likewise determined for each substance concentration, and the % inhibition of the AUC

compared with the control was calculated. On the basis of the % inhibition, the IC_{50} was calculated by nonlinear regression analysis according to the 4-parameter equation.

Table 1 shows the results.

Table 1:

Compound from example	Inhibition of platelet aggregation IC_{50} [micro M]	Compound from example	Inhibition of platelet aggregation IC_{50} [micro M]
1	0.65	2	1.6
5	8.5	7	0.158
16	0.127	66	0.025
77	0.009	85	0.059
90	0.012	98	0.334
108	0.016		

PAR1 binding test

The synthesized substances were examined in a PAR1 binding test. This tested whether the substances can inhibit the binding of a radioactively labeled PAR1 agonist known from the literature at the PAR1 receptor (Ho-Sam Ahn, Mol Pharm, 51:350-356, 1997).

The human PAR1 receptor was expressed transiently in High Five insect cells. From these cells, after 48 hours, a membrane preparation was produced by standard methods, aliquoted into 10 mM Tris-HCl; 0.3 mM EDTA; 1 mM EGTA; 250 mM sucrose pH 7.5, and stored at -80°C.

The substances were preincubated with the membrane at room temperature for 15 minutes, then the radioligand (ALA-(para-F-Phe)-Arg-ChA-homoArg-(3,4-^{3}H-Tyr)-NH_2; approx. 40 Ci/mMol) was added. The end concentration of the radioligand in the test buffer (50 mM Tris-HCl; 10 mM $MgCl_2$; 1 mM EGTA; 0.1 % BSA; 2% DMSO) was 20 nM, that of the membrane 1 mg/ml. After an incubation time of 60 minutes, 25 µL of the mixture were transferred to a 96-well MultiScreenHTS FB microtiter filtration plate (from Millipore), which had been pretreated beforehand with a 0.75% aqueous polyethyleneimine solution for

5 hours at room temperature. Thereafter, with vacuum extraction, each well was washed four times with 300 µL of buffer (50 mM Tris-HCl; 10 mM $MgCl_2$; 1 mM EGTA). The plate was then dried overnight, 100 µl of scintillator per well were added, and the plate was analyzed after 6 hours in a Wallac MicroBeta (from PerkinElmer) liquid scintillation counter. The nonspecific binding was determined in the presence of 100 µM SCH79797 (PAR-1 antagonist; from Tocris, Cat. No. 1592) and subtracted from all measurements. The 100% value used was a control without inhibitor. The % inhibition values of a substance dilution series were used to calculate the IC_{50} with the aid of nonlinear regression analysis according to the 4-parameter equation.

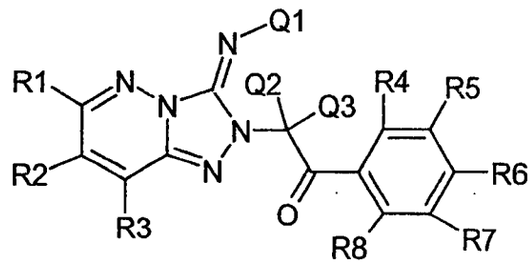
Table 2 shows the results.

Table 2:

Compound from example	Inhibition of binding IC_{50} [micro M]	Compound from example	Inhibition of binding IC_{50} [micro M]
14	0.279	178	0.126
26	1.1	186	0.119
50	0.631	197	0.149
56	24	199	0.206
76	0.951	207	0.174
84	9.8	215	0.219
89	0.107	221	0.155
101	1.4	222	0.416
117	0.098	230	0.234
127	2.5	236	1.4
144	0.827	239	0.113
161	0.365	240	0.484
163	0.364		
168	0.257		
174	0.183		

Claims

1. A compound of the formula I



(I)

and/or any stereoisomeric or tautomeric forms of the compound of the formula I and/or mixtures of these forms in any ratio, and/or a physiologically compatible salt of the compound of the formula I, where

Q1 is a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where alkyl and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

Q2 and Q3 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl or -(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R1, R2 and R3 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-C(O)-N(R11)-R12, -(C_0-C_4)-alkylene-C(O)-O-R11, -(C_0-C_4)-alkylene-C(O)-R11, -(C_0-C_4)-alkylene-N(R11)-R12, -(C_0-C_4)-alkylene-N(R11)-C(O)-R12, halogen, OH, -CN, -NO_2, -SO_2CH_3, -SO_2CF_3, -SF_5, -Si[-(C_1-C_4)-alkyl]$_3$, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or

trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl, -O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, -(C_4-C_{15})-Het, where Het is unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl or -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, -(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, -(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_3-C_6)-cycloalkyl, or

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R1 and R2 or R2 and R3, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of these atoms are replaced by nitrogen, oxygen or sulfur atoms, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine,

R11 and R12 are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or

-O-(C_3-C_6)-cycloalkyl,

-(C_0-C_4)-alkylene-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, $-SO_2CH_3$ or $-SO_2CF_3$, where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R11 and R12 in the "N(R11)-R12" and "N(R11)-C(O)-R12" fragments represent a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-C(O)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine,

R4, R5, R6, R7 and R8 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -CN, $-NO_2$, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(CO)-N(R21)-R22, $-SO_2CH_3$, $-SO_2CF_3$, -(C_0-C_4)-alkylene-C(O)-O-R21, halogen, $-SF_5$, -(C_0-C_4)-alkylene-C(O)-R21, -(C_0-C_4)-alkylene-N(R21)-R22, -(C_0-C_4)-alkylene-N(R21)-C(O)-R22, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -(C_0-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -Si[-(C_1-C_4)-alkyl]$_3$, -(C_0-C_6)-alkylene-O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, -(C_0-C_6)-alkylene-O-(C_0-C_6)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl, or -(C_4-C_{15})-Het where Het is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl,

-(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl,
where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, -(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen,
-(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or
-O-(C_3-C_6)-cycloalkyl,
-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl,
-(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or
-O-(C_3-C_6)-cycloalkyl,
where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or
R4 and R5, R5 and R6, R6 and R7 or R7 and R8, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of these atoms are replaced by nitrogen, oxygen or sulfur atoms, where the ring is unsubstituted or mono- or disubstituted independently by
-(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or
-O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine,
R21 and R22 are each independently a hydrogen atom, -(C_1-C_6)-alkyl,
-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by
-O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or
-O-(C_3-C_6)-cycloalkyl,
-(C_0-C_4)-alkylene-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen,
-(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or

-O-(C_3-C_6)-cycloalkyl,

-SO_2CH_3 or -SO_2CF_3,

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R21 and R22 in the "N(R21)-R22" and "N(R21)-C(O)-R22" fragments represent a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-C(O)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine.

2. A compound of the formula I as claimed in claim 1, wherein

Q1, Q2 and Q3 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl or -(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R1, R2 and R3 are the same or different and are each independently

a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -O-(C_1-C_8)-alkyl,

-O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-C(O)-N(R11)-R12,

-(C_0-C_4)-alkylene-C(O)-O-R11, -(C_0-C_4)-alkylene-C(O)-R11,

-(C_0-C_4)-alkylene-N(R11)-R12, -(C_0-C_4)-alkylene-N(R11)-C(O)-R12, halogen, OH,

-CN, -NO_2, -SO_2CH_3, -SO_2CF_3, -SF_5, -Si[-(C_1-C_4)-alkyl]$_3$,

-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl,

-O-(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl,

-(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl,

-O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, -(C_4-C_{15})-Het,

where Het is unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-

alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl,

where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, -(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen,

-(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl,

-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or -O-(C_3-C_6)-cycloalkyl, or

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine,

with the proviso that at least one R1, R2 or R3 is not a hydrogen atom or

R1 and R2 or R2 and R3, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of these atoms are replaced by nitrogen, oxygen or sulfur atoms, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring, in alkyl or cycloalkyl may be replaced by fluorine,

R11 and R12 are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl,

-(C_0-C_4)-alkylene-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen,

-(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or

-O-(C_3-C_6)-cycloalkyl

$-SO_2CH_3$ or $-SO_2CF_3$,

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R11 and R12 in the "N(R11)-R12" and "N(R11)-C(O)-R12" fragments represent a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-(CO)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R4, R5, R6, R7 and R8 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, OH,

-CN, $-NO_2$, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl,

-(C_0-C_4)-alkylene-(CO)-N(R21)-R22, $-SO_2CH_3$, $-SO_2CF_3$,

-(C_0-C_4)-alkylene-C(O)-O-R21, halogen, $-SF_5$,

-(C_0-C_4)-alkylene-C(O)-R21, -(C_0-C_4)-alkylene-N(R21)-R22,

-(C_0-C_4)-alkylene-N(R21)-C(O)-R22, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl,

-(C_0-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -Si[-(C_1-C_4)-alkyl]$_3$,

-(C_0-C_6)-alkylene-O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl,

-(C_0-C_6)-alkylene-O-(C_0-C_6)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl, or -(C_4-C_{15})-Het where Het is unsubstituted or mono-, di- or trisubstituted independently by -O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or -O-(C_3-C_6)-cycloalkyl,

where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, -(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or

pentasubstituted independently by halogen,
-(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or
-O-(C_3-C_6)-cycloalkyl,
-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl,
-(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or
-O-(C_3-C_6)-cycloalkyl, or
where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine,
with the proviso that at least one R4, R5, R6, R7 or R8 is not a hydrogen atom, or R4 and R5, R5 and R6, R6 and R7 or R7 and R8, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring, where the ring consists only of carbon atoms or 1, 2 or 3 of these atoms are replaced by nitrogen, oxygen or sulfur atoms, where the ring is unsubstituted or mono- or disubstituted independently by
-(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or
-O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine,
R21 and R22 are each independently a hydrogen atom, -(C_1-C_6)-alkyl,
-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di- or trisubstituted independently by
-O-(C_1-C_6)-alkyl, -(C_1-C_4)-alkyl, OH, -(C_3-C_6)-cycloalkyl or
-O-(C_3-C_6)-cycloalkyl,
-(C_0-C_4)-alkylene-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen,
-(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or
-O-(C_3-C_6)-cycloalkyl,
-SO_2CH_3 or -SO_2CF_3,
where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be

replaced by fluorine, or

R21 and R22 in the "N(R21)-R22" and "N(R21)-C(O)-R22" fragments represent a 5- to 8-membered ring which is formed together with the nitrogen atom "N" or the "N-C(O)" group to form cyclic amines, imides or lactams which contain up to 2 further heteroatoms from the group of N, O and S, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in the 5- to 8-membered ring formed, and in alkyl or cycloalkyl, may be replaced by fluorine.

3. A compound of the formula I as claimed in claim 1 or 2, wherein

Q1, Q2 and Q3 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl or -(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R1, R2 and R3 are the same or different and are each independently

a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-C(O)-N(R11)-R12, -(C_0-C_4)-alkylene-C(O)-O-R11, -(C_0-C_4)-alkylene-C(O)-R11, -(C_0-C_4)-alkylene-N(R11)-R12, -(C_0-C_4)-alkylene-N(R11)-C(O)-R12, halogen, OH, -CN, -NO_2, -SO_2CH_3, -Si[-(C_1-C_4)-alkyl]$_3$, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, -O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, -(C_4-C_{15})-Het or -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or

where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine,

with the proviso that at least one R1, R2 or R3 is not a hydrogen atom or

R1 and R2 or R2 and R3, together with the ring atoms to which they are each bonded,

form a ring selected from the group of 2,3,5,6,7,8-hexahydro-1,2,3a,4,5,8-hexaaza-cyclopenta[b]naphthalene; 2,6,7,8-tetrahydro-3H-5-oxa-1,2,3a,4,8-pentaaza-cyclopenta[b]naphthalene; 2,3,6,7-tetrahydro-5,8-dioxa-1,2,3a,4-tetraaza-cyclopenta[b]naphthalene; 2,3,6,7-tetrahydro-5H-8-oxa-1,2,3a,4,5-pentaaza-cyclopenta[b]naphthalene; 2,6,7,8-tetrahydro-3H-5-thia-1,2,3a,4,8-pentaaza-cyclopenta[b]naphthalene; 2,3,6,7,8,9-hexahydro-1,2,3a,4,6,9-hexaazacyclopenta[a]-naphthalene; 2,3-dihydro-5,7-dioxa-1,2,3a,4-tetraaza-s-indacene; 2,6,7,8-tetrahydro-3H-cyclopenta[e][1,2,4]triazolo[4,3-b]pyridazine; 2,7,8,9-tetrahydro-3H-cyclopenta[d][1,2,4]triazolo[4,3-b]pyridazine and 2,3,6a,9a-tetrahydro-[1,3]dioxolo[4,5-d][1,2,4]triazolo[4,3-b]pyridazine, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R11 and R12 are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl, -(C_0-C_4)-alkylene-(C_4-C_{15})-Het, -SO_2CH_3 or -SO_2CF_3, where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or

R11 and R12 in the "N(R11)-R12" and "N(R11)-C(O)-R12" fragments represent a 5- to 8-membered ring, selected from the group of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, morpholinyl, thiomorpholinyl, pyrrolidine-2.5-dionyl, piperidine-2,6-dionyl, piperazine-2,6-dionyl, morpholine-3,5-dionyl, pyrrolidin-2-onyl, piperidin-2-onyl, piperazin-2-onyl and morpholin-3-onyl, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,

R4, R5, R6, R7 and R8 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -CN, -NO_2, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl,

-(C_0-C_4)-alkylene-(CO)-N(R21)-R22, -SO_2CH_3, -SO_2CF_3,
-(C_0-C_4)-alkylene-C(O)-O-R21, halogen, -SF_5,
-(C_0-C_4)-alkylene-C(O)-R21, -(C_0-C_4)-alkylene-N(R21)-R22,
-(C_0-C_4)-alkylene-N(R21)-C(O)-R22, -(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl,
-(C_0-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -Si[-(C_1-C_4)-alkyl]$_3$,
-(C_0-C_6)-alkylene-O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl,
-(C_0-C_6)-alkylene-O-(C_0-C_6)-alkylene-(C_6-C_{14})-aryl or -(C_4-C_{15})-Het,
where alkyl, alkylene and cycloalkyl are each unsubstituted or mono-, di- or trisubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl, -(C_6-C_{14})-aryl where aryl is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen,
-(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or
-O-(C_3-C_6)-cycloalkyl,
-(C_4-C_{15})-Het where Het is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted independently by halogen, -(C_1-C_4)-alkyl,
-(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, or
-O-(C_3-C_6)-cycloalkyl, or
where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine,
with the proviso that at least one R4, R5, R6, R7 or R8 is not a hydrogen atom, or R4 and R5, R5 and R6, R6 and R7 or R7 and R8, together with the ring atoms to which they are each bonded, form a 5- to 8-membered ring selected from the group of 2,3-dihydrobenzo[1,4]dioxin; 3,4-dihydro-2H-benzo[1,4]oxazine; 1,2,3,4-tetrahydroquinoxaline; benzo[1,3]dioxole; 3,4-dihydro-2H-benzo[1,4]thiazine and 2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine,
where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine,
R21 and R22 are each independently a hydrogen atom, -(C_1-C_6)-alkyl,

-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-(C_6-C_{14})-aryl,
-(C_0-C_4)-alkylene-(C_4-C_{15})-Het, -SO_2CH_3 or -SO_2CF_3,
where some or all of the hydrogen atoms in alkyl, alkylene or cycloalkyl may be replaced by fluorine, or
R21 and R22 in the "N(R21)-R22" and "N(R21)-C(O)-R22" fragments represent a 5- to 8-membered ring selected from the group of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, morpholinyl, thiomorpholinyl, pyrrolidine-2.5-dionyl, piperidine-2,6-dionyl, piperazine-2,6-dionyl, morpholine-3,5-dionyl, pyrrolidin-2-onyl, piperidin-2-onyl, piperazin-2-onyl and morpholin-3-onyl, where the ring is unsubstituted or mono- or disubstituted independently by -(C_1-C_4)-alkyl, -(C_3-C_6)-cycloalkyl, OH, -O-(C_1-C_6)-alkyl or -O-(C_3-C_6)-cycloalkyl, where some or all of the hydrogen atoms in alkyl or cycloalkyl may be replaced by fluorine.

4. A compound of the formula I as claimed in claims 1 to 3, wherein
Q1, Q2 and Q3 are the same and are each a hydrogen atom,
R1, R2 and R3 are the same or different and are each independently
a hydrogen atom, -(C_1-C_6)-alkyl, -O-(C_1-C_8)-alkyl, -O-(C_3-C_6)-cycloalkyl, -(C_0-C_4)-alkylene-C(O)-N(R11)-R12, -(C_0-C_4)-alkylene-N(R11)-R12, halogen, -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -O-(C_0-C_4)-alkylenephenyl or -O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl,
where alkyl or alkylene is in each case unsubstituted or mono- or disubstituted by -O-(C_1-C_6)-alkyl,
where some or all of the hydrogen atoms in alkyl or alkylene may be replaced by fluorine,
with the proviso that at least one R1, R2 or R3 is not a hydrogen atom,
R11 and R12 are each independently a hydrogen atom or -(C_1-C_6)-alkyl, or
R11 and R12 in the "N(R11)-R12" fragment is a 5- to 8-membered ring selected from the group of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, imidazolyl, morpholinyl, thiomorpholinyl, pyrrolidine-2.5-dionyl, piperidine-2,6-dionyl, piperazine-2,6-dionyl, morpholine-3,5-dionyl, pyrrolidin-2-onyl, piperidin-2-onyl,

piperazin-2-onyl and morpholin-3-onyl,

R4, R5, R6, R7 and R8 are the same or different and are each independently a hydrogen atom, -(C_1-C_6)-alkyl, OH, -O-(C_1-C_8)-alkyl, halogen, -SF_5, -(C_0-C_4)-alkylene-N(R21)-R22, -(C_0-C_4)-alkylene-N(R21)-C(O)-R22, -CF_3, -(C_0-C_6)-alkylene-O-(C_1-C_6)-alkylene-O-(C_1-C_6)-alkyl, -(C_0-C_6)-alkylene-O-(C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, or -(C_0-C_6)-alkylene-O-(C_0-C_6)-alkylenephenyl,

where alkyl or alkylene is in each case unsubstituted or mono- or disubstituted by -O-(C_1-C_6)-alkyl,

with the proviso that at least one R4, R5, R6, R7 or R8 is not a hydrogen atom, or R4 and R5, R5 and R6, R6 or R7 or R7 and R8, together with the ring atoms to which they are each bonded, form a five- to eight-membered ring selected from the group of 2,3-dihydrobenzo[1,4]dioxin; 3,4-dihydro-2H-benzo[1,4]oxazine; 1,2,3,4-tetrahydro-quinoxaline; benzo[1,3]dioxole; 3,4-dihydro-2H-benzo[1,4]thiazine and 2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine,

where the ring is unsubstituted or mono- or disubstituted by -(C_1-C_4)-alkyl,

R21 and R22 are each independently a hydrogen atom or -(C_1-C_6)-alkyl, or

R21 and R22 in the "N(R21)-R22" fragment represent a 5- to 8-membered ring selected from the group of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, imidazolyl, morpholinyl, thiomorpholinyl, pyrrolidine-2,5-dionyl, piperidine-2,6-dionyl, piperazine-2,6-dionyl, morpholine-3,5-dionyl, pyrrolidin-2-onyl, piperidin-2-onyl, piperazin-2-onyl and morpholin-3-onyl.

5. A compound of the formula I as claimed in claims 1 to 4, wherein the compound of the formula I is selected from the group of 2-(6-chloro-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(3,5-di-tert-butyl-4-hydroxyphenyl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-isopropoxy-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-methoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 2-(6-ethoxy-3-imino-

[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(4-methoxy-3-morpholin-4-yl-5-trifluoromethylphenyl)ethanone, N-[3-[2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)acetyl]-5-(pentafluorosulfanyl)phenyl]-N-methylacetamide, N-[3-[2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)acetyl]-5-(pentafluorosulfanyl)phenyl]acetamide, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclopentyloxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclobutoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-phenoxy-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 2-(6-benzyloxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclohexyloxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[3-imino-6-(2,2,2-trifluoroethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-cyclopropylmethoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methylamino-5-(pentafluorosulfanyl)phenyl]ethanone, 2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone, 1-(3-tert-butyl-5-ethoxymethylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-cyclopropylmethoxymethylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-4,5-diethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-ethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-propoxymethylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-4,5-bis(cyclopropylmethoxy)phenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-

b]pyridazin-2-yl]-1-(3-methoxy-5-trifluoromethylphenyl)ethanone, 1-(3-tert-butyl-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-cyclopropylmethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-cyclobutylmethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-benzyloxymethyl-5-tert-butylphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-cyclo-hexylmethoxy-4,5-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 2-(6-butoxy-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-(3-tert-butyl-5-methoxymethylphenyl)ethanone, 1-(3-chloro-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(8-tert-butyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-piperidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-diethylamino-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-(3-isopropyl-5-methoxyphenyl)ethanone, 1-(3-cyclohexylmethoxy-5-ethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-bromo-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-[3-(3,3-dimethylbutoxy)-5-methoxyphenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-[3-(3,3-dimethylbutoxy)-5-ethoxyphenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-cyclohexylmethoxy-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-bromo-4,5-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 2-(6-diethylamino-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(3-imino-6-morpholin-4-yl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-imidazol-1-yl-3-imino-[1,2,4]triazolo[4,3-

b]pyridazin-2-yl)ethanone, 1-(5-bromo-2,3-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-methoxyphenyl)-2-{3-imino-6-[2-(2-methoxyethoxy)ethoxy]-[1,2,4]triazolo[4,3-b]pyridazin-2-yl}ethanone, 1-(3-chloro-4,5-dimethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-diethylamino-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-[3-tert-butyl-5-(2-methoxyethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-methoxyphenyl)-2-[3-imino-6-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-methoxymethylphenyl)-2-[3-imino-6-(2-methoxyethoxy)-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-morpholin-4-yl-5-(pentafluorosulfanyl)phenyl]ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-(5-methoxy-3-pentafluorosulfanylphenyl)ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-3-imino-[1,2,4]triazolo[4,3-b]-pyridazin-2-yl)ethanone, 1-[3-tert-butyl-5-(2-methoxyethoxymethyl)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-(2-methoxyethoxy)-5-(pentafluorosulfanyl)phenyl]ethanone, 2-(6-ethoxy-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone, 2-[6-(1-ethylpropoxy)-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]-1-[3-(3-methoxypropoxy)-5-(pentafluorosulfanyl)phenyl]ethanone, N,N-diethyl-2-[2-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-oxoethyl]-6-chloro-3-imino-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxamide, N,N-diethyl-6-chloro-3-imino-2-{2-[3-methoxy-5-(pentafluorosulfanyl)phenyl]-2-oxoethyl}-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-8-carboxamide, 2-(6-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-ethyl-3-imino-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, 1-[3-tert-butyl-5-(3-methoxypropoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-

imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-[3-tert-butyl-5-(2-methoxyethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-cyclopropylmethoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-(3-tert-butyl-5-methoxyphenyl)-2-[6-(1-ethylpropoxy)-3-imino-8-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 1-[3-tert-butyl-5-(3-methoxypropoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone, 2-(6-chloro-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)-1-[3-methoxy-5-(pentafluorosulfanyl)phenyl]ethanone, 1-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-(6-chloro-3-imino-7,8-dimethyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone, N,N-diethyl-6-chloro-3-imino-2-{2-[3-methoxy-5-(pentafluorosulfanyl)-phenyl]-2-oxoethyl}-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide, N,N-diethyl-2-[2-(3-tert-butyl-4-methoxy-5-morpholin-4-ylphenyl)-2-oxoethyl]-6-chloro-3-imino-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-7-carboxamide, 1-[3-tert-butyl-5-(3-methoxypropoxy)phenyl]-2-(6-ethoxy-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl)ethanone or 1-[3-tert-butyl-5-(2-methoxyethoxy)phenyl]-2-[6-(1-ethylpropoxy)-3-imino-7-methyl-[1,2,4]triazolo[4,3-b]pyridazin-2-yl]ethanone.

6. A medicament, characterized by an effective content of at least one compound of the formula I as claimed in one or more of claims 1 to 5 together with a pharmaceutically suitable and physiologically compatible carrier, additive and/or other active ingredients and excipients.

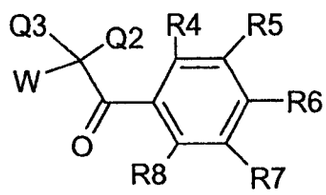
7. The use of the compound of the formula I as claimed in one or more of claims 1 to 5 for use in a method for prophylaxis, secondary prevention and treatment of all of those disorders associated with thromboses, embolisms, hypercoagulability, fibrotic changes or inflammatory disorders.

8. The use as claimed in claim 7, which is applied to myocardial infarction, angina pectoris and other types of acute coronary syndrome, stroke, peripheral vascular

disorders, deep vein thrombosis, pulmonary embolism, embolic or thrombotic events caused by cardiac arrhythmias, cardiovascular events such as restenosis following revascularization and angioplasty and similar procedures such as stent implantations and bypass operations or reduction of the risk of thrombosis following surgical procedures such as knee and hip joint operations or procedures leading to contact of blood with foreign surfaces, such as for dialysis patients and patients with indwelling catheters or disseminated intravascular coagulation, sepsis and other intravascular events associated with inflammation, atherosclerosis, diabetes and the metabolic syndrome and the sequelae thereof, tumor growth and tumor metastasis, inflammatory and degenerative articular disorders such as rheumatoid arthritis and arthrosis, impairments of the hemostatic system such as fibrin deposits, fibrotic changes in the lung such as chronic obstructive pulmonary disease, adult respiratory distress syndrome or fibrin deposits in the eye following eye operations or prevention and/or treatment of scarring.

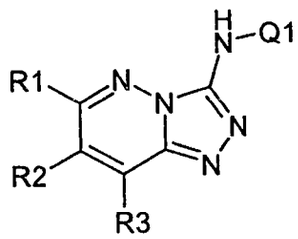
9. A process for preparing the compound of the formula I as claimed in one or more of claims 1 to 5, which comprises

a) reacting a compound of the formula II



(II)

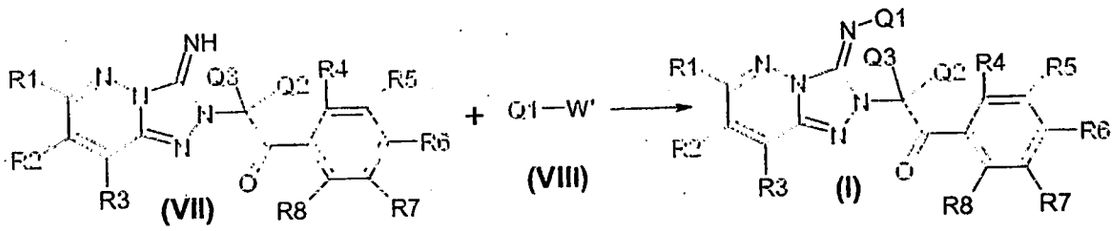
where R4 to R8, Q2 and Q3 are each as defined in formula I and W is chloride, bromide, mesylate or tosylate with a compound of the formula III



(III)

where R1, R2, R3 and Q1 are each as defined in formula I, with or without addition of base, in a solvent to give a compound of the formula I, or

b) reacting a compound of the formula VII



where R1, R2, R3, R4, R5, R6, R7, R8, Q1, Q2 and Q3 are each as defined in formula I with a compound Q-W' where W' is chloride, bromide, mesylate, tosylate, methylsulfate or a similar good leaving group, with or without addition of base, to give a compound of the formula I, or

c) either isolating the compound of the formula I prepared by method a) or b) in free form or releasing it from physiologically incompatible salts or, in the case of the presence of acidic or basic groups, converting it to physiologically compatible salts, or

d) separating a compound of the formula I prepared by method a) or b), or a suitable precursor of the formula I which, owing to its chemical structure, occurs in enantiomeric or diastereomeric forms, into the pure enantiomers or diastereomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and elimination of the chiral auxiliary groups.

000262

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/000406

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P7/02

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 391 451 A (EISAI CO LTD [JP]) 25 February 2004 (2004-02-25) cited in the application claims	1-9
A	EP 1 394 152 A (EISAI CO LTD [JP]) 3 March 2004 (2004-03-03) cited in the application claims	1-9
A	CHACKALAMANNIL S ET AL: "Thrombin receptor (PAR-1) antagonists as novel antithrombotic agents" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 16, no. 4, 1 April 2006 (2006-04-01), pages 493-505, XP002415653 ISSN: 1354-3776 page 497; compounds 13-15	1-9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 März 2009	12/03/2009

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/000406

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1391451 A	25-02-2004	BR 0208985 A	09-03-2004
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		CZ 20032824 A3	14-04-2004
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		EP 1394152 A1	03-03-2004
		HK 1086269 A1	07-11-2008
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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP2009/000406

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
INV. C07D487/04 A61K31/5025 A61P7/02

Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
C07D A61K A61P

Recherchierte, aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der Internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, BIOSIS, EMBASE

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP 1 391 451 A (EISAI CO LTD [JP]) 25. Februar 2004 (2004-02-25) in der Anmeldung erwähnt Ansprüche	1-9
A	EP 1 394 152 A (EISAI CO LTD [JP]) 3. März 2004 (2004-03-03) in der Anmeldung erwähnt Ansprüche	1-9
A	CHACKALAMANNIL S ET AL: "Thrombin receptor (PAR-1) antagonists as novel antithrombotic agents" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, Bd. 16, Nr. 4, 1. April 2006 (2006-04-01), Seiten 493-505, XP002415653 ISSN: 1354-3776 Seite 497; Verbindungen 13-15	1-9

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen ☒ Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
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Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kollmannsberger, M

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Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
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SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-95026

54. **TÍTULO** _____ 2/2

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51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** _____

DOMICILIO _____

74. **APODERADO** _____

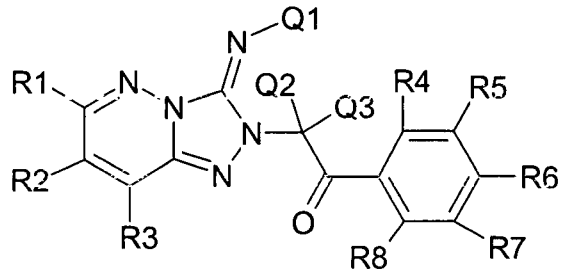
22. **BOGOTÁ, D.C.,** _____

(FORMA P-10)

000266

Triazolopiridazinas como inhibidores de PAR1, su producción y su uso como medicamentos

La invención se refiere a nuevos compuestos de la fórmula I



(I)

donde cada uno de R1, R2, R3, R4, R5, R6, R7, R8, Q1, Q2 y Q3 es como se define más adelante. Los compuestos de la fórmula I tienen actividad antitrombótica e inhiben especialmente el receptor 1 activado por proteasa (PAR1). La invención también se refiere a un proceso para preparar el compuesto de la fórmula I y a su uso como un medicamento.

El receptor 1 activado por proteasas (PAR1) es un receptor de trombina que pertenece a la clase de los receptores acoplados a proteína G (GPCR = siglas en inglés). El gen de PAR1 está situado en el cromosoma 5q13, consiste en dos exones y cubre una región de aproximadamente 27 kb.

El PAR1 se expresa, entre otras, en células endoteliales, células de la musculatura lisa, fibroblastos, neuronas y plaquetas de sangre humana. En las plaquetas sanguíneas, PAR1 es un receptor importante de la transmisión de señales y está implicado en el inicio de la agregación de las plaquetas sanguíneas.

La activación de los PAR se realiza por la eliminación proteolítica de parte del extremo N de los PAR, quedando expuesta de esta manera una nueva secuencia N-terminal que activa el receptor (Pharmacol Rev 54:203-217, 2002).

La coagulación sanguínea es un proceso para controlar el flujo sanguíneo que es esencial para la supervivencia de los mamíferos. El proceso de coagulación y la posterior fragmentación del coágulo después de que tenga lugar la curación de la herida comienza después del daño del vaso y se puede dividir en cuatro fases:

1. La fase de constricción vascular: de esta manera se reduce la pérdida de sangre en el área dañada.

2. La siguiente fase es la de la adhesión de las plaquetas al colágeno expuesto en el subendotelio. Esta adhesión primaria a la matriz activa a las plaquetas, que después secretan diversos activadores que conducen al

aumento de la activación. Estos activadores además estimulan el reclutamiento adicional de nuevas plaquetas hasta el sitio de la lesión del vaso y promueven la agregación de las plaquetas. Las plaquetas se agregan en el sitio del daño de la pared del vaso y forman un tapón plaquetario todavía suelto. La activación de las plaquetas también conduce a la presentación de fosfatidilserina y fosfatidilinositol a lo largo de las superficies de la membrana celular. La exposición de estos fosfolípidos es esencial para la unión y activación de los complejos multienzimáticos de la cascada de la coagulación.

3. El agregado plaquetario aún suelto inicialmente se entrecruza por fibrina. Si el trombo solo comprende plaquetas y fibrina, es un trombo blanco: Si adicionalmente están presentes corpúsculos rojos de la sangre, es un trombo rojo.

4. Después de la curación de la herida, el trombo se disgrega por la acción de la proteína plasmina.

Dos rutas alternativas dan lugar a la formación de un coágulo de fibrina, la ruta intrínseca y la extrínseca. Estas rutas se inician por mecanismos diferentes, pero en una fase posterior convergen para dar un tramo común de la ruta de la cascada de la coagulación. La formación de un trombo rojo o un coágulo basada en una anormalidad de la pared de los vasos sin una herida es el resultado de la ruta intrínseca. La formación del coágulo de fibrina como respuesta al daño tisular o a una lesión es el resultado de la ruta extrínseca. Ambas rutas incluyen un número relativamente grande de proteínas, que se conocen como factores de la coagulación.

La ruta intrínseca requiere los factores de la coagulación VIII, IX, X, XI y XII y precalicreína, cininógeno de alto peso molecular, iones calcio y fosfolípidos de las plaquetas. Cada una de estas proteínas conduce a la activación del factor X.

La ruta intrínseca se inicia cuando la precalicreína, cininógeno de alto peso molecular factor XI y XII se unen a una superficie cargada negativamente. Este momento se denomina fase de contacto. La exposición al colágeno de la pared del vaso es el estímulo principal de la fase de contacto. El resultado de los procesos de la fase de contacto es la conversión de precalicreína en calicreína, que a su vez activa al factor XII. El factor XIIa hidroliza adicionalmente la precalicreína para dar calicreína, de manera que el resultado es la activación. Según aumenta la activación del factor XII hay una activación del factor XI que conduce a una

liberación de bradicinina, un vasodilatador. De esta manera termina la fase inicial de vasoconstricción. La bradicinina se produce a partir del cininógeno de alto peso molecular. En presencia de iones Ca^{2+}, el factor XIa activa el factor IX. El factor IX es una proenzima, que contiene restos de c-carboxiglutamato (GLA, por sus siglas en inglés) dependientes de vitamina K. La actividad serina proteasa se vuelve evidente después de que los iones Ca^{2+} se hayan unido a estos restos de GLA. Varias serina proteasas de la cascada de la coagulación de la sangre (factores II, VII, IX y X) contienen dichos restos GLA dependientes de la vitamina K. El factor IXa escinde el factor X y conduce a la activación al factor Xa. La condición previa para la formación del factor IXa es la formación de un complejo proteasa a partir de iones Ca^{2+} y los factores VIIIa, IXa y X sobre la superficie de las plaquetas activadas. Una de las reacciones de las plaquetas activadas es la presentación de fosfatidilserina y fosfatidilinositol a lo largo de las superficies. La formación del complejo proteasa se hace posible por exposición de estos fosfolípidos. En este proceso, el factor VIII actúa como un receptor para los factores IXa y X. El factor VIII por lo tanto representa un cofactor en la cascada de la coagulación. La activación del factor VIII con formación del factor VIIIa, el receptor real, solamente requiere una cantidad mínima de trombina. Según aumenta la concentración de trombina, el factor VIIIa se escinde finalmente más y se inactiva por la trombina. Esta actividad doble de la trombina en relación con el factor VIII conduce a la formación del complejo proteasa que es autolimitante y estando localizada de esta manera la coagulación sanguínea.

El PAR1 y PAR4 juegan un papel central en la activación de las plaquetas de sangre humana por trombina; la activación de estos receptores conduce a cambios morfológicos en las plaquetas sanguíneas, liberación de ADP y agregación de las plaquetas de la sangre (Nature 413:26-27, 2001).

Se describen inhibidores de PPAR1, por ejemplo, en las solicitudes de patente europea EP1391451 o EP1391452, en las solicitudes de patente americana US 6.063.847 y US 2004/152736 y en la solicitud internacional WO 03/089428.

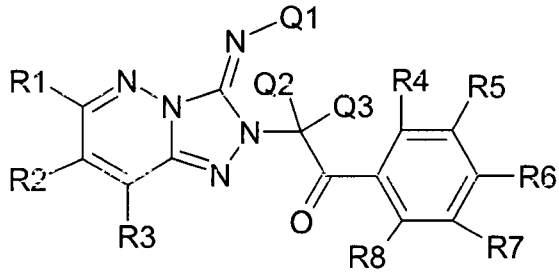
Los compuestos de la fórmula I muestran una alta inhibición específica del receptor 1 activado por proteasa y son notables, en comparación con los compuestos del documento EP1391451, por una mejor permeabilidad de la membrana, por ejemplo a través de células de la pared intestinal, que puede contribuir a una mejor biodisponibilidad.

Por lo tanto, los compuestos de la fórmula I son adecuados para el uso

profiláctico y terapéutico en seres humanos que padecen trastornos asociados con trombosis, embolias, hipercoagulabilidad o alteraciones fibróticas. Son ejemplos de tales enfermedades trombosis, trombosis venosa profunda, embolias pulmonares, infarto cerebral, infarto de miocardio, presión sanguínea alta, trastornos inflamatorios, reumatismo, asma, glomerulonefritis u osteoporosis. Los compuestos de la fórmula I pueden emplearse para la prevención secundaria y son adecuados tanto para la terapia aguda como para la terapia a largo plazo.

Los compuestos de la fórmula I también pueden emplearse junto con ingredientes activos que actúan por principios antitrombóticos diferentes de PAR1.

1) Por lo tanto, la invención se refiere a un compuesto de la fórmula I



(I)

y/o cualquier forma estereoisomérica o tautomérica del compuesto de la fórmula I y/o mezclas de estas formas en cualquier proporción, y/o una sal fisiológicamente compatible del compuesto de la fórmula I, en la que

Q1 es un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde cada uno de alquilo y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

Q2 y Q3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6) o -cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

R1, R2 y R3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-C(O)-N(R11)-R12, -alquileno (C_0-C_4)-C(O)-O-R11, -alquileno (C_0-C_4)-C(O)-R11, -alquileno (C_0-C_4)-N(R11)-R12, -alquileno (C_0-C_4)-N(R11)-C(O)-R12, halógeno, OH, -CN, -NO_2, -SO_2CH_3, -SO_2CF_3, -SF_5, -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_1-C_6)-O-alquilo

(C_1-C_6), -O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}), donde Het está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-alquileno (C_1-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6),

donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-cicloalquilo (C_3-C_6), o

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R1 y R2 o R2 y R3, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

cada uno de R11 y R12 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -SO_2CH_3 o -SO_2CF_3,

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R11 y R12 en los fragmentos "N(R11)-R12" y "N(R11)-C(O)-R12" representan un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-C(O)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

R4, R5, R6, R7 y R8 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), OH, -CN, -NO_2, -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-(CO)-N(R21)-R22, -SO_2CH_3, -SO_2CF_3, -alquileno (C_0-C_4)-C(O)-O-R21, halógeno, -SF_5, -alquileno (C_0-C_4)-C(O)-R21, -alquileno (C_0-C_4)-N(R21)-R22, -alquileno (C_0-C_4)-N(R21)-C(O)-R22, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -alquileno (C_0-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_0-C_6)-O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -alquileno (C_0-C_6)-O-alquileno (C_0-C_6)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), o -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-(C_3-C_6)-cicloalquilo,
donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R4 y R5, R5 y R6, R6 y R7 o R7 y R8, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

cada uno de R21 y R22 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), $-SO_2CH_3$ o $-SO_2CF_3$, donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R21 y R22 en los fragmentos "N(R21)-R22" y "N(R21)-C(O)-R22" representan un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-C(O)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor.

2) Se da preferencia a un compuesto de la fórmula I en la que

Q1, Q2 y Q3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6) o -cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

R1, R2 y R3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -O-alquilo (C_1-C_8), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-C(O)-N(R11)-R12, -alquileno

(C_0-C_4)-C(O)-O-R11, -alquileno (C_0-C_4)-C(O)-R11, -alquileno (C_0-C_4)-N(R11)-R12, -alquileno (C_0-C_4)-N(R11)-C(O)-R12, halógeno, OH, -CN, $-NO_2$, $-SO_2CH_3$, $-SO_2CF_3$, $-SF_5$, -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}), donde Het está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-alquileno (C_1-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6),

donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-cicloalquilo (C_3-C_6), o

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor,

con la condición de que al menos un R1, R2 o R3 no sea un átomo de hidrógeno o R1 y R2 o R2 y R3, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el anillo de 5 a 8 miembros, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

cada uno de R11 y R12 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo

(C_3-C_6), -alquileno (C_0-C_4)-Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), $-SO_2CH_3$ o $-SO_2CF_3$,

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R11 y R12 en los fragmentos "N(R11)-R12" y "N(R11)-C(O)-R12" representan un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-(CO)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

R4, R5, R6, R7 y R8 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), OH, -CN, $-NO_2$, -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-(CO)-N(R21)-R22, $-SO_2CH_3$, $-SO_2CF_3$, -alquileno (C_0-C_4)-C(O)-O-R21, halógeno, $-SF_5$, -alquileno (C_0-C_4)-C(O)-R21, -alquileno (C_0-C_4)-N(R21)-R22, -alquileno (C_0-C_4)-N(R21)-C(O)-R22, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -alquileno (C_0-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_0-C_6)-O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -alquileno (C_0-C_6)-O-alquileno (C_0-C_6)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), o -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o

-O-cicloalquilo (C_3-C_6), o

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor,

con la condición de que al menos un R4, R5, R6, R7 o R8 no sea un átomo de hidrógeno, o

R4 y R5, R5 y R6, R6 y R7 o R7 y R8, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

cada uno de R21 y R22 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), $-SO_2CH_3$ o $-SO_2CF_3$, donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R21 y R22 en los fragmentos "N(R21)-R22" y "N(R21)-C(O)-R22" representan un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-C(O)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor.

3) Se da preferencia particular a un compuesto de la fórmula I en la que

Q1, Q2 y Q3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6) o -cicloalquilo (C_3-C_6), donde algunos o todos

los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

R1, R2 y R3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-C(O)-N(R11)-R12, -alquileno (C_0-C_4)-C(O)-O-R11, -alquileno (C_0-C_4)-C(O)-R11, -alquileno (C_0-C_4)-N(R11)-R12, -alquileno (C_0-C_4)-N(R11)-C(O)-R12, halógeno, OH, -CN, -NO_2, -SO_2CH_3, -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_0-C_4)-arilo (C_6-C_{14}), -O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) o -O-alquileno (C_1-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6),

donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor,

con la condición de que al menos un R1, R2 o R3 no sea un átomo de hidrógeno o

R1 y R2 o R2 y R3, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo seleccionado entre el grupo de 2,3,5,6,7,8-hexahidro-1,2,3a,4,5,8-hexaaza-ciclopenta[b]naftaleno; 2,6,7,8-tetrahidro-3H-5-oxa-1,2,3a,4,8-pentaaza-ciclopenta[b]naftaleno; 2,3,6,7-tetrahidro-5,8-dioxa-1,2,3a,4-tetraaza-ciclopenta[b]naftaleno; 2,3,6,7-tetrahidro-5H-8-oxa-1,2,3a,4,5-pentaaza-ciclopenta[b]naftaleno; 2,6,7,8-tetrahidro-3H-5-tia-1,2,3a,4,8-pentaaza-ciclopenta[b]naftaleno; 2,3,6,7,8,9-hexahidro-1,2,3a,4,6,9-hexaaza-ciclopenta[a]naftaleno; 2,3-dihidro-5,7-dioxa-1,2,3a,4-tetraaza-s-indaceno; 2,6,7,8-tetrahidro-3H-ciclopenta[e][1,2,4]triazolo[4,3-b]piridazina; 2,7,8,9-tetrahidro-3H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazina y 2,3,6a,9a-tetrahidro-[1,3]dioxolo[4,5-d][1,2,4]triazolo[4,3-b]piridazina, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

cada uno de R11 y R12 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}), -alquileno (C_0-C_4)-Het (C_4-C_{15}), -SO_2CH_3 o -SO_2CF_3,

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R11 y R12 en los fragmentos "N(R11)-R12" y "N(R11)-C(O)-R12" representan un anillo de 5 a 8 miembros seleccionado entre el grupo de azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, azepinilo, morfolinilo, tiomorfolinilo, pirrolidina-2,5-dionilo, piperidina-2,6-dionilo, piperazina-2,6-dionilo, morfolina-3,5-dionilo, pirrolidin-2-onilo, piperidin-2-onilo, piperazin-2-onilo y morfolin-3-onilo, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6) donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

R4, R5, R6, R7 y R8 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), OH, -CN, -NO_2, -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-(CO)-N(R21)-R22, -SO_2CH_3, -SO_2CF_3, -alquileno (C_0-C_4)-C(O)-O-R21, halógeno, -SF_5, -alquileno (C_0-C_4)-C(O)-R21, -alquileno (C_0-C_4)-N(R21)-R22, -alquileno (C_0-C_4)-N(R21)-C(O)-R22, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -alquileno (C_0-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_0-C_6)-O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -alquileno (C_0-C_6)-O-alquileno (C_0-C_6)-arilo (C_6-C_{14}) o -Het (C_4-C_{15}),
donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-cicloalquilo (C_3-C_6), o
donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor,

con la condición de que al menos un R4, R5, R6, R7 o R8 no sea un átomo de hidrógeno, o

R4 y R5, R5 y R6, R6 y R7 o R7 y R8, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros

seleccionado entre el grupo de 2,3-dihidrobenzo[1,4]dioxina; 3,4-dihidro-2H-benzo[1,4]oxazina; 1,2,3,4-tetrahidro-quinoxalina; benzo[1,3]dioxol; 3,4-dihidro-2H-benzo[1,4]tiazina y 2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepina, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

cada uno de R21 y R22 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}), -alquileno (C_0-C_4)-Het (C_4-C_{15}), $-SO_2CH_3$ o $-SO_2CF_3$, donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R21 y R22 en los fragmentos "N(R21)-R22" y "N(R21)-C(O)-R22" representan un anillo de 5 a 8 miembros seleccionado entre el grupo de azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, azepinilo, morfolinilo, tiomorfolinilo, pirrolidina-2,5-dionilo, piperidina-2,6-dionilo, piperazina-2,6-dionilo, morfolina-3,5-dionilo, pirrolidin-2-onilo, piperidin-2-onilo, piperazin-2-onilo y morfolin-3-onilo, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor.

4) La invención también se refiere a un compuesto de la fórmula I, en la que

Q1, Q2 y Q3 son iguales y cada uno es un átomo de hidrógeno,

R1, R2 y R3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-C(O)-N(R11)-R12, -alquileno (C_0-C_4)-N(R11)-R12, halógeno, -O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquilenofenilo (C_0-C_4) o -O-alquileno (C_1-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6),
donde el alquilo o alquileno, en cada caso, está sin sustituir o mono- o disustituido con -O-alquilo (C_1-C_6),
donde algunos o todos los átomos de hidrógeno en el alquilo o alquileno pueden reemplazarse por flúor,

con la condición de que al menos un R1, R2 o R3 no sea un átomo de hidrógeno,

cada uno de R11 y R12 es independientemente un átomo de hidrógeno o -alquilo (C_1-C_6), o

R11 y R12 en el fragmento "N(R11)-R12" es un anillo de 5 a 8 miembros seleccionado entre el grupo de azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, azepinilo, imidazolilo, morfolinilo, tiomorfolinilo, pirrolidina-2,5-dionilo, piperidina-2,6-dionilo, piperazina-2,6-dionilo, morfolina-3,5-dionilo, pirrolidin-2-onilo, piperidin-2-onilo, piperazin-2-onilo y morfolin-3-onilo,

R4, R5, R6, R7 y R8 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), OH, -O-alquilo (C_1-C_6), halógeno, -SF_5, -alquileno (C_0-C_4)-N(R21)-R22, -alquileno (C_0-C_4)-N(R21)-C(O)-R22, -CF_3, -alquileno (C_0-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -alquileno (C_0-C_6)-O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6) o -alquileno (C_0-C_6)-O-alquilenofenilo (C_0-C_6),

donde el alquilo o alquileno, en cada caso, está sin sustituir o mono- o disustituido con -O-alquilo (C_1-C_6),

con la condición de que al menos un R4, R5, R6, R7 o R8 no sea un átomo de hidrógeno, o

R4 y R5, R5 y R6, R6 o R7 o R7 y R8, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de cinco a ocho miembros seleccionado entre el grupo de 2,3-dihidrobenzo[1,4]dioxina; 3,4-dihidro-2H-benzo[1,4]oxazina; 1,2,3,4-tetrahidro-quinoxalina; benzo[1,3]dioxol; 3,4-dihidro-2H-benzo[1,4]tiazina y 2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepina, donde el anillo está sin sustituir o mono- o disustituido con -alquilo (C_1-C_4),

cada uno de R21 y R22 es independientemente un átomo de hidrógeno o -alquilo (C_1-C_6), o

R21 y R22 en el fragmento "N(R21)-R22" representan un anillo de 5 a 8 miembros seleccionado entre el grupo de azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, azepinilo, imidazolilo, morfolinilo, tiomorfolinilo, pirrolidina-2,5-dionilo, piperidina-2,6-dionilo, piperazina-2,6-dionilo, morfolina-3,5-dionilo, pirrolidin-2-onilo, piperidin-2-onilo, piperazin-2-onilo y morfolin-3-onilo.

5) Se prefieren excepcionalmente compuestos de la fórmula I que incluyen los siguientes compuestos:

2-(6-cloro-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(3,5-di-terc-butil-4-hidroxifenil)etanona,

1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-isopropoxi-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,

1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-metoxi-[1,2,4]triazolo[4,3-

b]piridazin-2-il)etanona,
2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(4-metoxi-3-morfolin-4-il-5-trifluorometilfenil)etanona,
N-[3-[2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-acetil]-5-(pentafluorosulfanil)fenil]-N-metilacetamida,
N-[3-[2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-acetil]-5-(pentafluorosulfanil)fenil]acetamida en forma de la sal del ácido trifluoroacético,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona en forma de la sal del ácido trifluoroacético,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclopentiloxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclobutoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-fenoxi-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
2-(6-benciloxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclohexiloxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[3-imino-6-(2,2,2-trifluoroetoxi)-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona en forma de la sal del ácido trifluoroacético,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclopropilmetoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metilamino-5-(pentafluorosulfanil)fenil]etanona,
2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona,
1-(3-terc-butil-5-etoximetilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-5-ciclopropilmetoximetilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-4,5-dietoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-

b]piridazin-2-il]etanona,
1-(3-terc-butil-5-etoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-5-propoximetilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-4,5-bis(ciclopropilmetoxi)fenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(3-metoxi-5-trifluorometilfenil)etanona,
1-(3-terc-butil-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-5-ciclopropilmetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-5-ciclobutilmetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-benciloximetil-5-terc-butilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-ciclohexilmetoxi-4,5-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
2-(6-butoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(3-terc-butil-5-metoximetilfenil)etanona,
1-(3-cloro-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-6-il)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona en forma de la sal del ácido trifluoroacético,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-piperidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-dietilamino-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(3-isopropil-5-metoxifenil)etanona,
1-(3-ciclohexilmetoxi-5-etoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-bromo-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-

2-il]etanona,
1-[3-(3,3-dimetilbutoxi)-5-metoxifenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-[3-(3,3-dimetilbutoxi)-5-etoxifenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-ciclohexilmetoxi-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-bromo-4,5-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
2-(6-dietilamino-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-morfolin-4-il-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-imidazol-1-il-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
1-(5-bromo-2,3-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-5-metoxifenil)-2-{3-imino-6-[2-(2-metoxietoxi)etoxi]-[1,2,4]triazolo[4,3-b]piridazin-2-il}etanona,
1-(3-cloro-4,5-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-dietilamino-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona en forma de la sal del ácido trifluoroacético,
1-[3-terc-butil-5-(2-metoxietoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-5-metoxifenil)-2-[3-imino-6-(2-metoxietoxi)-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-5-metoximetilfenil)-2-[3-imino-6-(2-metoxietoxi)-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-morfolin-4-il-5-(pentafluorosulfanil)fenil]etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-3-imino-8-metil-

[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(5-metoxi-3-pentafluorosulfanilfenil)etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
1-[3-terc-butil-5-(2-metoxietoximetil)fenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-(2-metoxietoxi)-5-(pentafluorosulfanil)fenil]etanona,
2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona,
2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-(3-metoxipropoxi)-5-(pentafluorosulfanil)fenil]etanona,
N,N-dietil-2-[2-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-oxoetil]-6-cloro-3-imino-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida,
N,N-dietil-6-cloro-3-imino-2-{2-[3-metoxi-5-(pentafluorosulfanil)fenil]-2-oxoetil}-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida,
2-(6-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,
1-[3-terc-butil-5-(3-metoxipropoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-[3-terc-butil-5-(2-metoxietoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-5-ciclopropilmetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-(3-terc-butil-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
1-[3-terc-butil-5-(3-metoxipropoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona,
2-(6-cloro-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona,
1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona,

N,N-dietil-6-cloro-3-imino-2-{2-[3-metoxi-5-(pentafluorosulfanil)fenil]-2-oxoetil}-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida,
N,N-dietil-2-[2-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-oxoetil]-6-cloro-3-imino-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida,
1-[3-terc-butil-5-(3-metoxipropoxi)fenil]-2-(6-etoxi-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona o
1-[3-terc-butil-5-(2-metoxietoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona.

La expresión "alquilo (C_1-C_4)" o "alquilo (C_1-C_6)" pretende indicar radicales de hidrocarburo cuya cadena de carbonos es una cadena lineal o ramificada y contiene de 1 a 4 átomos de carbono o de 1 a 6 átomos de carbono, por ejemplo metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, 2,3-dimetilbutilo o neohexilo.

La expresión "-alquileno (C_0-C_4)" o "-alquileno (C_1-C_6)" pretende indicar radicales de hidrocarburo cuya cadena de carbonos es una cadena lineal o ramificada y contiene de 1 a 4 o 1-6 átomos de carbono, por ejemplo metileno, etileno, 1-metilmetileno, propileno, 1-metiletileno, butileno, 1-propilmetileno, 1-etil-1-metilmetileno, 1,2-dimetiletileno, 1,1-dimetilmetileno, 1-etiletileno, 1-metilpropileno, 2-metilpropileno, pentileno, 1-metilbutileno, hexileno, 1-metilpentileno. "-Alquileno C_0" es un enlace covalente.

La expresión "-O-alquilo (C_1-C_6)" o "-O-alquilo (C_1-C_8)" pretende indicar radicales alcoxi cuya cadena de carbonos es una cadena lineal o ramificada y contiene de 1 a 6 o de 1 a 8 átomos de carbono, por ejemplo metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, terc-butoxi, 1-pentoxi, 2-pentoxi, 3-pentoxi, 1-hexoxi, 2-hexoxi, 3-hexoxi, 1-heptoxi, 2-heptoxi, 3-heptoxi, 4-heptoxi, 2,4-dimetilpentan-3-oxi, 1-octoxi, 2-octoxi, 3-octoxi, 2,2,4-trimetilpentan-3-oxi, 2,3,4-trimetilpentan-3-oxi o 4-octoxi.

La expresión "cicloalquilo (C_3-C_6)" pretende indicar radicales tales como compuestos que se obtienen a partir de monociclos de 3 a 6 miembros tales como ciclopropano, ciclobutano, ciclopentano o ciclohexano.

La expresión "-O-cicloalquilo (C_3-C_6)" pretende indicar radicales cicloalcoxi tales como compuestos que se obtienen a partir de monociclos de 3 a 6 miembros tales como ciclopropoxi, ciclobutoxi, ciclopentoxi o ciclohexoxi.

La expresión "-arilo (C_6-C_{14})" pretende indicar radicales de hidrocarburo aromáticos que tienen de 6 a 14 átomos de carbono en el anillo. Son radicales -arilo

(C_6-C_{14}), por ejemplo, fenilo, naftilo, por ejemplo 1-naftilo, 2-naftilo, antrilo o fluorenilo. Los radicales naftilo y, en especial, fenilo, son radicales arilo preferidos.

La expresión "Het" pretende indicar sistemas de anillos que tienen de 4 a 15 átomos de carbono que están presentes en uno, dos o tres sistemas de anillos unidos entre sí y que, de acuerdo con el tamaño del anillo, pueden contener uno, dos, tres o cuatro heteroátomos iguales o diferentes del grupo de oxígeno, nitrógeno y azufre. Son ejemplos de estos sistemas de anillos radicales acridinilo, azepinilo, azetidinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzisoxazolilo, bencisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, cromanilo, cromenilo, cinolinilo, decahidroquinolinilo, dibenzofuranilo, dibenzotiofenilo, dihidrofuran[2,3-b]-tetrahidrofuranoílo, dihidrofuranilo, dioxolilo, dioxanilo, 2H,6H-1,5,2-ditiazinilo, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isoquinolinilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isotiazolidinilo, 2-isotiazolinilo, isotiazolilo, isoxazolilo, isoxazolidinilo, 2-isoxazolinilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidinilo, oxazolilo, oxotiolanilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, purinilo, piranilo, pirazinilo, piroazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridotiofenilo, piridilo, pirimidinilo, pirrolidinilo, pirrolinilo, 2H-pirrolilo, pirrolilo, tetrahidrofuranoílo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, tetrahidropiridinilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, tiazolidinilo, tiazolinilo, tiazolilo, tienilo, tienoimidazolilo, tienooxazolilo, tienopirrolilo, tienopiridilo, tienotiazolilo, tienotiofenilo, tiomorfolinilo, triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo o xantenilo.

La expresión "R1 y R2 o R2 y R3, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre" pretende indicar, por ejemplo, sistemas de anillos tales como 2,3,5,6,7,8-hexahidro-1,2,3a,4,5,8-hexaaza-ciclopenta[b]naftaleno; 2,6,7,8-tetrahidro-3H-5-oxa-1,2,3a,4,8-pentaaza-ciclopenta[b]naftaleno; 2,3,6,7-tetrahidro-5,8-dioxa-1,2,3a,4-tetraaza-

ciclopenta[b]naftaleno; 2,3,6,7-tetrahidro-5H-8-oxa-1,2,3a,4,5-pentaaza-ciclopenta[b]naftaleno; 2,6,7,8-tetrahidro-3H-5-tia-1,2,3a,4,8-pentaaza-ciclopenta[b]naftaleno; 2,3,6,7,8,9-hexahidro-1,2,3a,4,6,9-hexaaza-ciclopenta[a]-naftaleno; 2,3-dihidro-5,7-dioxa-1,2,3a,4-tetraaza-s-indaceno; 2,6,7,8-tetrahidro-3H-ciclopenta[e][1,2,4]triazolo[4,3-b]piridazina; 2,7,8,9-tetrahidro-3H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazina o 2,3,6a,9a-tetrahidro-[1,3]dioxolo[4,5-d][1,2,4]-triazolo[4,3-b]piridazina.

La expresión "R4 y R5, R5 y R6, R6 o R7 o R7 y R8, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre" pretende indicar, por ejemplo, sistemas de anillos tales como 2,3-dihidrobenzo[1,4]dioxina; 3,4-dihidro-2H-benzo[1,4]oxazina; 1,2,3,4-tetrahidroquinoxalina; benzo[1,3]dioxol; 3,4-dihidro-2H-benzo[1,4]tiazina o 2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepina.

Las expresiones "R11 y R12 en los fragmentos "N(R11)-R12" y "N(R11)-C(O)-R12" representa un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-(CO)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S" o "R11 y R12 en los fragmentos "N(R21)-R22" y "N(R21)-C(O)-R22" es un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-(CO)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S" pretenden indicar, por ejemplo, sistemas de anillos tales como aminas cíclicas tales como azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, azepinilo, imidazolilo, morfolinilo o tiomorfolinilo, y en el caso de los radicales de imidas tales como pirrolidina-2,5-dionilo, piperidina-2,6-dionilo, piperazina-2,6-dionilo, morfolina-3,5-dionilo, y en el caso de los radicales de lactamas tales como pirrolidin-2-onilo, piperidin-2-onilo, piperazin-2-onilo, morfolin-3-onilo.

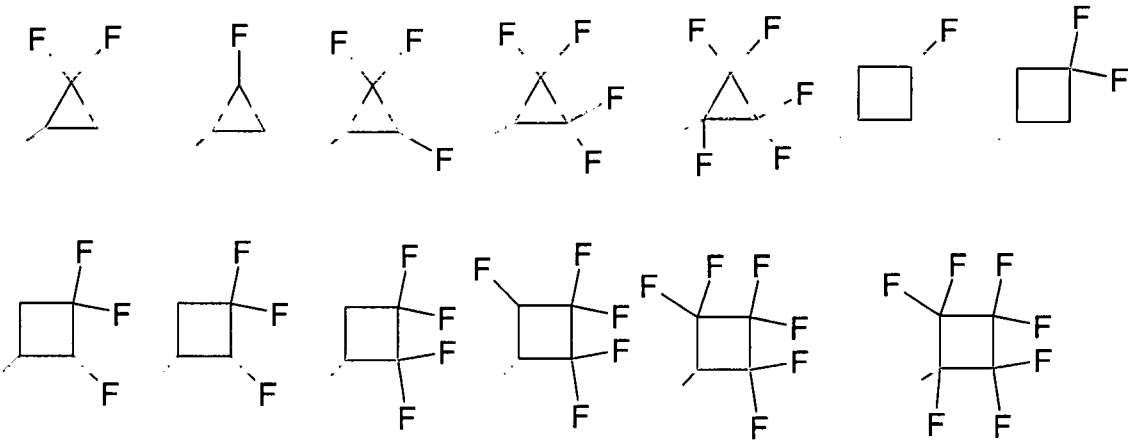
La expresión reordenada "alquilo, alquileno o cicloalquilo en el que algunos o todos los átomos de hidrógeno se reemplazan por flúor" pretende indicar un alquilo, alquileno o cicloalquilo parcialmente fluorado o perfluorado que se obtiene, por ejemplo, para alquilo, a partir de los siguientes radicales: $-CF_3$, $-CHF_2$, $-CH_2F$, $-CHF-CF_3$, $-CHF-CHF_2$,

$-CHF-CH_2F$, $-CH_2-CF_3$, $-CH_2-CHF_2$, $-CH_2-CH_2F$, $-CF_2-CF_3$, $-CF_2-CHF_2$,

$-CF_2-CH_2F$, $-CH_2-CHF-CF_3$, $-CH_2-CHF-CHF_2$, $-CH_2-CHF-CH_2F$,

$-CH_2-CH_2-CF_3$, $-CH_2-CH_2-CHF_2$, $-CH_2-CH_2-CH_2F$, $-CH_2-CF_2-CF_3$, $-CH_2-CF_2-CHF_2$, $-CH_2-CF_2-CH_2F$, $-CHF-CHF-CF_3$, $-CHF-CHF-CHF_2$, $-CHF-CHF-CH_2F$, $-CHF-CH_2-CF_3$, $-CHF-CH_2-CHF_2$, $-CHF-CH_2-CH_2F$, $-CHF-CF_2-CF_3$, $-CHF-CF_2-CHF_2$, $-CHF-CF_2-CH_2F$, $-CF_2-CHF-CF_3$, $-CF_2-CHF-CHF_2$, $-CF_2-CHF-CH_2F$, $-CF_2-CH_2-CF_3$, $-CF_2-CH_2-CHF_2$, $-CF_2-CH_2-CH_2F$, $-CF_2-CF_2-CF_3$, $-CF_2-CF_2-CHF_2$, $-CF_2-CF_2-CH_2F$, $-CH(CF_3)_2$, $-CH(CHF_2)_2$, $-CH(CFH_2)_2$, $-CH(CFH_2)(CHF_2)$, $-CH(CFH_2)(CF_3)$, $-CH(CFH_2)(CH_3)$, $-CH(CHF_2)(CH_3)$, $-CH(CF_3)(CH_3)$, $-CF(CF_3)_2$, $-CF(CHF_2)_2$, $-CF(CFH_2)_2$, $-CF(CFH_2)(CHF_2)$, $-CF(CFH_2)(CF_3)$, $-CF(CFH_2)(CH_3)$, $-CF(CHF_2)(CH_3)$ o $-CF(CF_3)(CH_3)$, y además las posibles combinaciones adicionales para butilo, pentilo y hexilo, que, al igual que propilo, también pueden estar ramificadas,

para alquileno, por ejemplo, a partir de los siguientes radicales: $-CF_2-$, -CHF-, $-CHF-CF_2-$, -CHF-CHF-, $-CHF-CH_2-$, $-CF_2-CF_2-$ o $-CF_2-CH_2F$, y también las posibles combinaciones adicionales para propileno, butileno, pentileno y hexileno, que también pueden estar ramificadas, y para cicloalquilo, por ejemplo, a partir de los radicales



y también los anillos ciclopentilo y ciclohexilo análogos más grandes.

La expresión "halógeno" pretende indicar flúor, cloro, bromo o yodo, dándose preferencia a flúor, cloro o bromo, especialmente a flúor o cloro.

Las expresiones descritas anteriormente también pueden combinarse según se desee, como se hace, por ejemplo, en "-alquileno (C_0-C_6)-O-alquileno (C_0-C_6)-arilo (C_6-C_{14})".

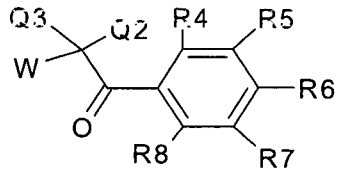
Los grupos funcionales de los intermedios utilizados, por ejemplo grupos amino o carboxilo en los compuestos de la fórmula I, pueden estar enmascarados

por grupos protectores adecuados. Los grupos protectores adecuados para las funciones amino son, por ejemplo, el grupo t-butoxicarbonilo, benciloxicarbonilo o ftaloílo, y también el grupo protector de tritilo o tosilo. Los grupos protectores adecuados para la función carboxilo son, por ejemplo, ésteres de alquilo, arilo o arilalquilo. Los grupos protectores pueden introducirse y retirarse por técnicas que son bien conocidas o se describen en la presente memoria (véase Greene, T. W., Wuts, P. G. M., Protective Groups in Organic Synthesis (1999), 3ª Ed., Wiley-Interscience, o Kocienski, P. J., Protecting Groups (2004), 3ª Ed., Thieme. La expresión "grupo protector" también puede incluir grupos protectores unidos a los polímeros correspondientes.

Los compuestos de la invención se pueden preparar por procedimientos conocidos o por procedimientos descritos en esta memoria.

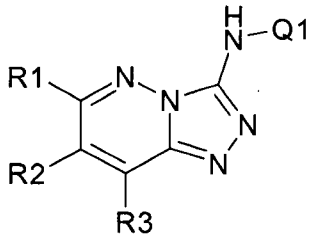
La invención se refiere además a un procedimiento para preparar el compuesto de la fórmula I y/o una forma estereoisomérica del compuesto de la fórmula I y/o una sal fisiológicamente compatible del compuesto de la fórmula I, que comprende

a) hacer reaccionar un compuesto de la fórmula II



(II)

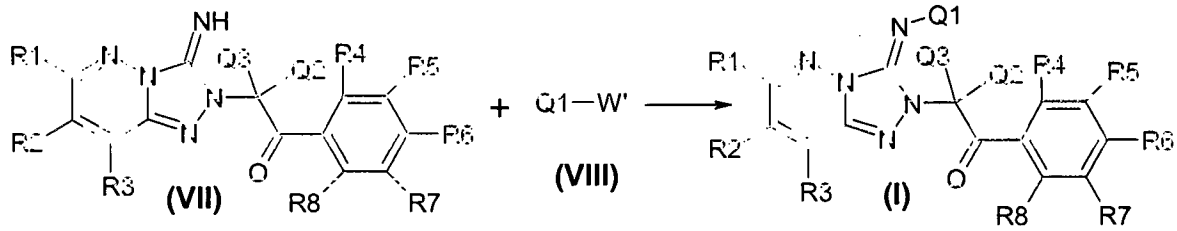
en la que cada uno de R4, R5, R6, R7, R8, Q2 y Q3 es como se ha definido en la fórmula I y W es cloruro, bromuro, mesilato o tosilato con un compuesto de la fórmula III



(III)

en la que cada uno de R1, R2, R3 y Q1 es como se ha definido en la fórmula I, con o sin la adición de una base, en un disolvente para dar un compuesto de la fórmula I, o

b) hacer reaccionar un compuesto de la fórmula VII



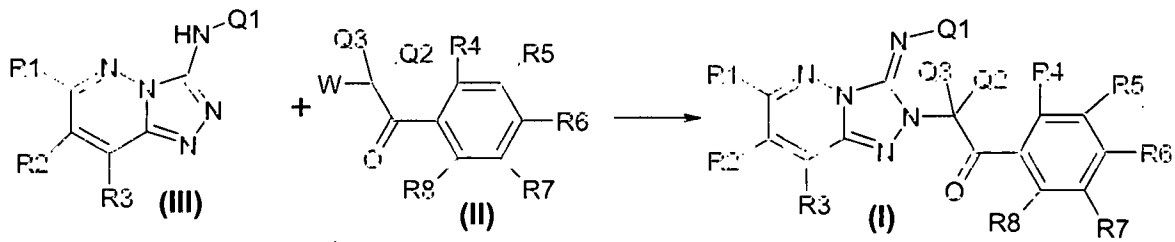
en la que cada uno de R1, R2, R3, R4, R5, R6, R7, R8, Q1, Q2 y Q3 es como se ha definido en la fórmula I con un compuesto Q-W' en el que W' es cloruro, bromuro, mesilato, tosilato, metilsulfato o un grupo saliente adecuado similar, con o sin la adición de una base, para dar un compuesto de la fórmula I, o

c) aislar el compuesto de la fórmula I preparado por el método a) o b) en forma libre o liberarlo de sales fisiológicamente incompatibles o, en el caso de que haya presencia de grupos ácidos o básicos, convertirlo en sales fisiológicamente compatibles, o

d) separar un compuesto de la fórmula I preparado por el método a) o b), o un precursor adecuado de la fórmula I que, debido a su estructura química, se da en formas enantioméricas o diastereoméricas, en los enantiómeros o diastereómeros puros por formación de sal con ácidos o bases enantioméricamente puras, cromatografía sobre fases estacionarias quirales o derivatización por medio de compuestos enantioméricamente puros quirales tales como aminoácidos, separación de los diastereómeros obtenidos de esa manera y eliminación de los grupos auxiliares quirales.

La invención se refiere adicionalmente a un proceso para preparar el compuesto de la fórmula I de acuerdo con el esquema 1.

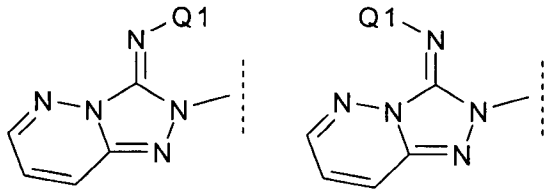
Esquema 1:



Los reactivos II y III, III que está presente opcionalmente en forma de una sal, se convierten a temperatura ambiente o a una temperatura ligeramente elevada de 40°Ca 60°C, ventajosamente, cuando III está en forma de una sal, en presencia de una base, preferiblemente una base de Hünig, en un disolvente, preferiblemente

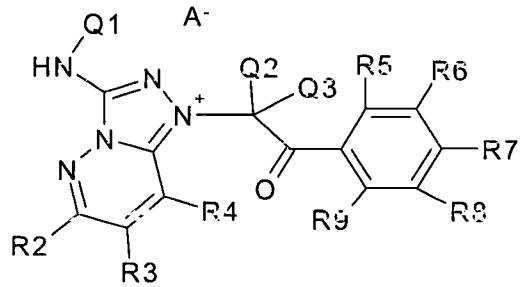
dimetilformamida (DMF) o dioxano, para dar el compuesto de la fórmula I. Cada uno de los radicales R1, R2, R3, R4, R5, R6, R7, R8, Q1, Q2 y Q3 es como se ha definido en la fórmula I y W representa un grupo saliente adecuado tal como cloruro, bromuro, mesilato o tosilato, preferiblemente bromuro o mesilato.

Algunos de los compuestos de la fórmula I pueden darse en formas isoméricas, en cuyo caso Q1 en la siguiente subfórmula de la fórmula I puede tener la configuración (E) o (Z):



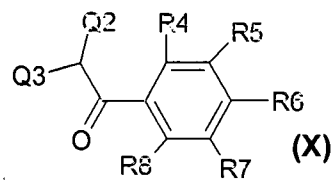
(E) (Z)

Las sales de triazolopiridazinio 1-sustituidas (A) que se forman igualmente en diferentes proporciones en estas condiciones de reacción de acuerdo con el patrón de sustitución pueden retirarse por cromatografía o por cristalización. Es ventajoso realizar la sepración por medio de gel de sílice con diclorometano-metanol como mezcla de eluyentes.

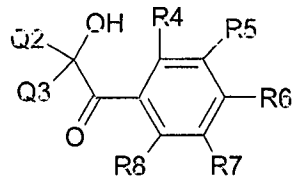


(A)

Los compuestos de la fórmula II pueden obtenerse en el mercado o por métodos bibliográficos, por ejemplo procediendo a partir de las acetofenonas correspondientes X o X' (véase, por ejemplo: Phosphorus and Sulfur and the Related Elements (1985), 25(3), 357 o Tetrahedron Letters (1984), 25(34), 3715). Los compuestos bien conocidos del tipo X pueden funcionalizarse, por ejemplo, en el grupo acetilo con, entre otros reactivos, bromo o cloro elemental, derivados de tribromuro tales como tribromuro de feniltrimetilamonio, 1,3-diclorodimetilhidantoína, N-cloro- o N-bromosuccinimida. Los compuestos del tipo X' pueden convertirse, por ejemplo, usando cloruro de mesilo o tosilo, en los compuestos del tipo II.

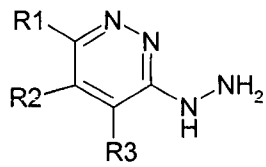


(X)

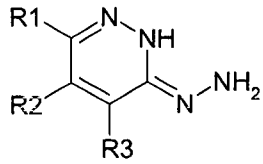


(X')

Los compuestos de la fórmula III pueden obtenerse en el mercado o por métodos bibliográficos. Los precursores adecuados son compuestos del tipo XX, que pueden ciclarse en presencia de bromuro de cianógeno, cloruro de cianógeno o cianuro de tosilo para dar compuestos del tipo III, y que también pueden estar presentes en la forma tautomérica del tipo XXa.



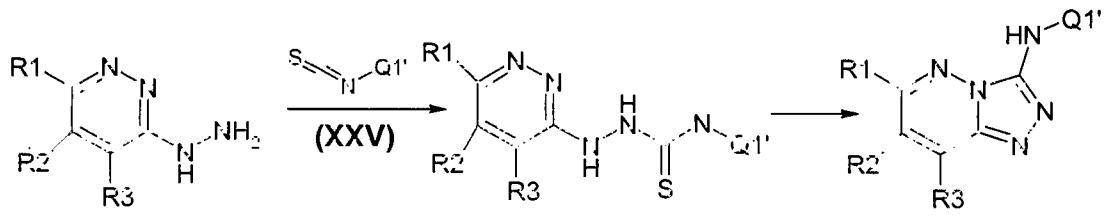
(XX)



(XXa)

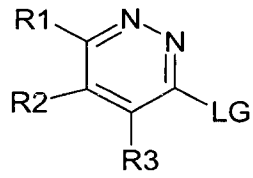
El compuesto de la fórmula XX tal como piridazin-3-ilhidrazina y el compuesto de la fórmula XXa tal como [2H-piridazin-(3E)-ilideno]hidrazina son formas tautoméricas. Cuando sólo se utiliza una notación en lo sucesivo en la presente memoria, esto significa que también se describe la otra forma tautomérica.

Como alternativa, los compuestos del tipo XX también pueden hacerse reaccionar con isotiocianatos del tipo XXV para dar las tioureas del tipo XXVI. Estas últimas, después de la activación del azufre, por ejemplo con cloruro de tosilo, una carbodiimida, bromoacetato de etilo u óxido de mercurio, pueden convertirse en los compuestos del tipo de la fórmula III. Aquí, cada uno de los radicales R1, R2 y R3 es como se ha definido anteriormente y Q1' corresponde a Q1 o a un grupo protector tal como FMOC(fluoren-9-ilmetiloxicarbonilo), que, después del cierre del anillo, puede eliminarse de nuevo, y de esta manera pueden obtenerse compuestos en los que Q1 es hidrógeno.



(XX) (XXVI) (III)

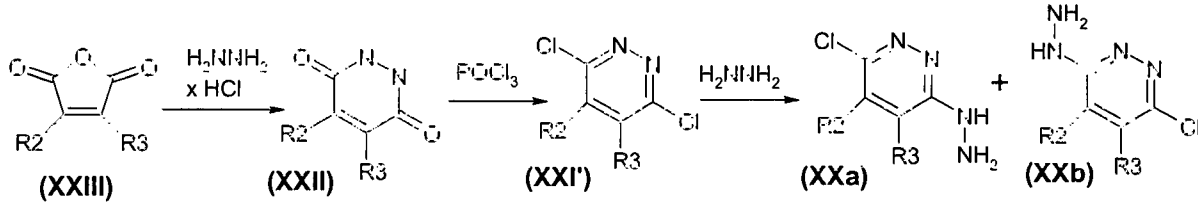
Los compuestos del tipo XX pueden obtenerse incorporando hidrazina en compuestos del tipo XXI, que están disponibles en el mercado con una gran diversidad de patrones de sustitución diferentes. Aquí, cada uno de los radicales



(XXI)

R1, R2 y R3 es como se ha definido anteriormente y LG representa un grupo saliente adecuado tal como flúor, cloro, bromo, yodo, mesilato, tosilato, triflato o nonaflato.

Una ruta para los compuestos de cloro del tipo XXI' es, por ejemplo, la reacción de anhídridos maleicos del tipo XXIII con hidrocloruro de hidrazina para dar los compuestos del tipo XXII, seguido de la reacción con oxicloruro de fósforo para dar el dicloruro XXI' y con hidrazina para dar los compuestos del tipo XXa y XXb.



Un compuesto de la fórmula I preparado de acuerdo con el esquema 1, o un precursor de la fórmula I adecuado que debido a su estructura química se da en formas enantioméricas, puede separarse en los enantiómeros puros por formación de sal utilizando ácidos o bases enantioméricamente puras, cromatografía sobre fases estacionarias quirales o derivatización por medio de compuestos quirales enantioméricamente puros tales como aminoácidos, separación de los diastereómeros obtenidos de esta manera y eliminación de los grupos quirales auxiliares (proceso c), o el compuesto de la fórmula I preparado de acuerdo con el esquema 1 puede aislarse en forma libre o, en el caso de que haya presencia de grupos ácidos o básicos, convertirse en sales fisiológicamente compatibles (proceso d).

Los productos ácidos o básicos del compuesto de fórmula I pueden estar en forma de sus sales o en la forma libre. Se prefieren sales farmacológicamente aceptables, por ejemplo sales de metales alcalinos o alcalinotérreos o hidrocloruros, sulfatos, hemisulfatos, metilsulfonatos, p-toluensulfonatos, todos los posibles fosfatos, y sales de aminoácidos, bases naturales o ácidos carboxílicos tales como lactatos, citratos, tartratos, acetatos, adipatos, fumaratos, gluconatos, glutamatos, maleatos o pamoatos.

Las sales fisiológicamente toleradas se preparan a partir de compuestos de fórmula I que pueden formar sales, incluyendo sus formas estereoisoméricas, en la etapa de proceso c) de una manera conocida per se. Si los compuestos de la fórmula I contienen funcionalidades ácidas, se pueden formar sales estables de metales alcalinos, de metales alcalinotérreos o sales de amonio opcionalmente sustituido, con reactivos básicos tales como hidróxidos, carbonatos, bicarbonatos, alcóxidos y amoníaco o bases orgánicas, por ejemplo trimetilamina o trietilamina, etanolamina, dietanolamina o trietanolamina, trometamol o incluso aminoácidos básicos, por ejemplo lisina, ornitina o arginina. Los grupos básicos de los compuestos de la fórmula I forman sales de adición de ácidos con ácidos. Son adecuados para este fin tanto ácidos inorgánicos como ácidos orgánicos, tales como ácido clorhídrico o bromhídrico, sulfúrico, hemisulfúrico, fosfórico, metansulfónico, bencensulfónico, p-toluensulfónico, 4-bromobencensulfónico, ciclohexilamidosulfónico, trifluorometilsulfónico, 2-hidroxietansulfónico, acético, oxálico, tartárico, succínico, glicerolfosfórico, láctico, málico, adípico, cítrico, fumárico, maleico, glucónico, glucurónico, palmítico o trifluoroacético.

En la etapa d) del procedimiento, el compuesto de la fórmula I, si se presenta como una mezcla de diastereoisómeros o enantiómeros o se forma como mezclas de los mismos en la síntesis elegida, se separa en los estereoisómeros puros, bien por cromatografía sobre un material de soporte opcionalmente quiral, o bien, si el compuesto racémico de la fórmula I es capaz de la formación de sales, también es posible llevar a cabo una cristalización fraccionada de las sales diastereoisoméricas formadas utilizando una base o ácido ópticamente activos como un auxiliar. Ejemplos de fases estacionarias quirales adecuadas para la separación cromatográfica de enantiómeros en capa fina o en columna, son los soportes de gel de sílice modificados (llamados fases de Pirkle) y los carbohidratos de alto peso molecular tales como triacetilcelulosa. Para fines analíticos, también es posible utilizar métodos cromatográficos de gases sobre fases estacionarias quirales después de una derivatización apropiada, conocida por los expertos en la técnica. Para separar los enantiómeros de los ácidos carboxílicos racémicos, se forman las sales diastereoisoméricas con diferente solubilidad con una base ópticamente activa, que normalmente está comercializada, tal como (-)-nicotina, (+)- y (-)-feniletilamina, bases de quinina, L-lisina o L- y D-arginina, se aísla el componente menos soluble como un sólido, se deposita el diastereoisómero más soluble de las aguas madre, y se obtienen los enantiómeros puros de las sales

diastereoisoméricas obtenidas de esta manera. De la misma forma es posible, en principio, convertir los compuestos racémicos de fórmula I que contienen un grupo básico, como un grupo amino, con ácidos ópticamente activos, como ácido (+)-canfor-10-sulfónico, ácido D- y L-tartárico, ácido D- y L-láctico y ácido (+) y (-)-mandélico, para producir los enantiómeros puros. También es posible convertir compuestos quirales que contienen funciones alcohol o amina con aminoácidos enantioméricamente puros apropiadamente activados, o cuando sea apropiado protegidos en N, en los correspondientes ésteres o amidas, o a la inversa, los ácidos carboxílicos quirales con aminoácidos enantioméricamente puros protegidos en el carboxilo, se pueden convertir en las amidas, o con ácidos hidroxi-carboxílicos enantioméricamente puros, tales como ácido láctico, en los correspondientes ésteres quirales. La quiralidad del resto aminoácido o alcohol que se ha introducido en las formas enantioméricamente puras se puede utilizar también para separar los isómeros llevando a cabo una separación de los diastereoisómeros que están ahora disponibles por cristalización o cromatografía sobre fases estacionarias adecuadas, y eliminando después el resto quiral incluido por métodos adecuados.

Otra posibilidad con alguno de los compuestos de la invención es preparar las estructuras flanqueantes usando materiales de partida diastereoisoméricamente o enantioméricamente puros. Por lo tanto, también es posible emplear otros procesos o procesos simplificados para purificar los productos finales. Estos materiales de partida se han preparado previamente de una forma enatiomérica o diastereoisoméricamente pura mediante procedimientos conocidos de la bibliografía. Esto puede significar, en concreto, que se emplean procesos enantioselectivos en la síntesis de las estructuras básicas, o también se puede realizar una separación de enantiómeros (o diastereómeros) en una etapa temprana de la síntesis y no en la etapa de los productos finales. De forma similar, puede lograrse una simplificación de estas separaciones actuando en dos o más etapas.

La invención se refiere también a medicamentos que tienen un contenido eficaz de al menos un compuesto de la fórmula I y/o de una sal fisiológicamente tolerada del compuesto de la fórmula I y/o de una forma opcionalmente estereoisomérica del compuesto de la fórmula I, junto con un vehículo farmacéuticamente adecuado y fisiológicamente tolerado, aditivos y/o otros ingredientes activos y excipientes.

Debido a las propiedades farmacológicas, los compuestos de la invención

son adecuados, por ejemplo, para la profilaxis, prevención secundaria y terapia de todos los trastornos que pueden tratarse por inhibición del receptor 1 activado por proteasa (PAR1). Por lo tanto, los compuestos de la invención son adecuados tanto para uso profiláctico como para uso terapéutico en seres humanos. Son adecuados tanto para el tratamiento agudo como para la terapia a largo plazo. Los compuestos de la fórmula I se pueden emplear en pacientes que padecen trastornos del bienestar o enfermedades asociadas con trombosis, embolias, hipercoagulabilidad, cambios fibróticos o trastornos inflamatorios.

Éstos incluyen infarto de miocardio, angina de pecho y todos los demás tipos de síndrome coronario agudo, accidentes cerebrovasculares, trastornos vasculares periféricos, trombosis de venas profundas, embolia pulmonar, acontecimientos embólicos o trombóticos provocados por arritmias cardíacas, acontecimientos cardiovasculares como reestenosis después de una revascularización, angioplastia y procedimientos similares como implantes de endoprótesis vasculares y operaciones de bypass. Los compuestos de la fórmula I se pueden emplear adicionalmente en todos los procedimientos que llevan al contacto de la sangre con superficies extrañas, tales como para pacientes de diálisis y pacientes con catéteres permanentes. Los compuestos de la fórmula I se pueden emplear para reducir el riesgo de trombosis después de procedimientos quirúrgicas tales como operaciones de articulaciones de rodilla y de cadera.

Los compuestos de la fórmula I son adecuados para el tratamiento de pacientes con coagulación intravascular diseminada, sepsis y otros acontecimientos intravasculares asociados con la inflamación. Además, los compuestos de la fórmula I son adecuados para la profilaxis y el tratamiento de pacientes con aterosclerosis, diabetes y el síndrome metabólico y sus secuelas. Los trastornos del sistema hemostático (por ejemplo depósitos de fibrina) se han implicado en mecanismos que conducen al crecimiento tumoral y metástasis tumoral, y en trastornos articulares inflamatorios y degenerativos tales como artritis reumatoide y artrosis. Los compuestos de la fórmula I son adecuados para retrasar o prevenir estos procesos.

Otras indicaciones para el uso de los compuestos de la fórmula I son cambios fibróticos del pulmón, tales como la enfermedad pulmonar obstructiva crónica, el síndrome de insuficiencia respiratoria del adulto (ARDS, por sus siglas en inglés) y del ojo, como los depósitos de fibrina después de operaciones oculares. Los compuestos de la fórmula I también son adecuados para la prevención y/o

tratamiento de la formación de cicatrices.

Los medicamentos de la invención pueden administrarse mediante la vía oral, por inhalación, rectal o transdérmica, o mediante inyección subcutánea, intraarticular, intraperitoneal o intravenosa. Se prefiere la administración oral. Es posible el recubrimiento de endoprótesis vasculares con compuestos de la fórmula I y de otras superficies que entran en contacto con la sangre en el cuerpo. La invención también se refiere a un proceso para fabricar un medicamento, que comprende preparar una forma de dosificación adecuada de al menos un compuesto de fórmula I con un vehículo farmacéuticamente adecuado y fisiológicamente tolerado y, cuando resulte apropiado, más ingredientes activos, aditivos o excipientes adecuados.

Las formulaciones farmacéuticas o sólidas adecuadas son, por ejemplo, gránulos, polvos, comprimidos revestidos, comprimidos, (micro)cápsulas, supositorios, jarabes, disoluciones, suspensiones, emulsiones, gotas o disoluciones inyectables, y productos con liberación retardada del ingrediente activo, en cuya producción se utilizan adyuvantes habituales como vehículos, disgregantes, ligantes, agentes de revestimiento, agentes de hinchamiento, deslizantes o lubricantes, aromas, edulcorantes y solubilizantes. Son excipientes que se utilizan frecuentemente, y que se pueden mencionar, el carbonato de magnesio, dióxido de titanio, lactosa, manitol y otros azúcares, talco, proteínas lácteas, gelatina, almidón, celulosa y sus derivados, aceites animales y vegetales, tales como aceite de hígado de pescado, aceite de girasol, de cacahuete o de sésamo, polietilenglicol y disolventes tales como, por ejemplo, agua estéril y alcoholes monohidroxílicos o polihidroxílicos, tales como glicerol.

Los productos farmacéuticos se fabrican y administran preferiblemente en unidades de dosificación, en las que cada unidad comprende, como ingrediente activo, una dosis concreta del compuesto de la invención de fórmula I. En el caso de unidades de dosificación sólidas, tales como comprimidos, cápsulas, comprimidos revestidos o supositorios, esta dosis puede ascender hasta aproximadamente 1000 mg, pero con preferencia se sitúa en aproximadamente 50 a 300 mg y, en el caso de disoluciones inyectables en forma de ampollas puede ascender hasta aproximadamente 300 mg, pero con preferencia se sitúa en aproximadamente 10 a 100 mg.

Las dosis diarias indicadas para el tratamiento de un paciente adulto que pese aproximadamente 70 kg son, dependiendo de la actividad del compuesto de

fórmula I, desde aproximadamente 2 mg a 1000 mg del ingrediente activo, preferiblemente desde aproximadamente 50 mg a 500 mg. Sin embargo, en algunas circunstancias, también pueden resultar apropiadas unas dosis diarias mayores o menores. La dosis diaria puede administrarse mediante una única administración en forma de una unidad de dosificación unitaria, o también una pluralidad de unidades de dosificación más pequeñas, o mediante una administración múltiple de dosis divididas en intervalos concretos.

Los compuestos de la fórmula I pueden administrarse como monoterapia y junto con todos los antitrombóticos (anticoagulantes e inhibidores de la agregación plaquetaria), trombolíticos (activadores de plasminógeno de cualquier tipo), otras sustancias que tengan actividad profibrinolítica, antihipertensivos, reguladores de la glucosa sanguínea, agentes que disminuyen los lípidos y antiarrítmicos. Son inhibidores de la agregación plaquetaria a este respecto inhibidores de la ciclooxigenasa 1 tales como aspirina, antagonistas irreversibles de $P2Y_{12}$ tales como clopidogrel o prasugrel, antagonistas reversibles de $P2Y_{12}$ tales como cangrelor o AZD6140 y antagonistas de tromboxano A_2/prostaglandina H_2 tales como terutroban. Ha sido posible mostrar efectos aditivos del bloqueo de PAR1 junto con el boqueo de $P2Y_{12}$ por ejemplo (Eur. Heart J. 2007, 28, Abstract Supplement, 188).

Ejemplos

Los productos finales se caracterizaron generalmente por un método cromatográfico con detección de ultravioleta y espectrometría de masas (acoplamiento de LCUV/ESI-MS) y ^{1}H RMN. Los compuestos se describen indicando el tiempo de retención correspondiente en la corriente iónica (ta LC-MS) y la señal de $M+H^+$ correspondiente en el caso de ionización positiva en el espectro de masas correspondiente. Cuando no pudo obtenerse ninguna señal de masa de $M+H^+$, los datos de ^{1}H RMN se indicaron como una alternativa. Las abreviaturas usadas o bien están explicadas o bien corresponden a las convenciones usuales.

Las separaciones con Gel de Sílice se realizaron manualmente (cromatografía ultrarrápida) o se soportaron en sistemas de cartucho semiautomáticos tales como Companion (CombiFlash) o Flashmaster II (Jones Chromatography). A menos que se indique otra cosa, las separaciones cromatográficas se realizaron sobre gel de sílice con mezclas de acetato de etilo/heptano, diclorometano/etanol o diclorometano/metanol como eluyente.

Los disolventes se evaporaron generalmente a presión reducida de 35°Ca

45ºCen un evaporador rotatorio, a lo que se hace referencia mediante expresiones tales como "liberación del disolvente", "concentrado", "concentrado por evaporación rotatoria", "secado", "disolvente eliminado o retirado" o expresiones similares.

Los análisis de LCUV/MS se realizaron en las siguientes condiciones:

Método A (=met. a):

Sistema:	Agilent 1100 HPLC-System acoplado a 1100 LC/MSD
Columna:	YMCJ´shere ODS H80 20 x 2,1 mm, material de carga 4 µm
Eluyente:	ACN:H_2O+TFA al 0,05% (caudal 1 ml/min)
Gradiente:	4:96 (0 min) → 95:5 (2 min) → 95:5 (2,4 min) → 4:96 (2,45 min)
Ionización:	ESI+

Método B (=met. b):

Sistema:	Agilent 1200 HPLC-System acoplado a 6120 LC/MS
Columna:	Luna C18, 10 x 2,0 mm, material de carga 3 µm
Eluyente:	ACN:H_2O+TFA al 0,05% (caudal 1,1 ml/min)
Gradiente:	7:93 (0 min) → 95:5 (1 min) (95:5 (1,45 min) (7:93 (1,5 min)
Ionización:	ESI+

Método C (=met. c):

Sistema:	Agilent 1200 HPLC-System acoplado a 6120 LC/MS
Columna:	Luna C18, 10 x 2,0 mm, material de carga 3 □m
Eluyente:	ACN:H2O+TFA al 0,05% (caudal 1,1 ml/min)
Gradiente:	1:99 (0 min) (7:93 (0,3 min) (95:5 (1,3 min) (95:5 (1,75 min) (1:99 (1,8 min)
Ionización:	ESI+

Método D (=met. d):

Sistema:	Waters: bomba 1525, 996 PDA, LCT classic TOF-MS
Columna:	Waters XBridge C18 4,6 x 50 mm; 2,5 □M
Eluyente:	ACN + TFA al 0,05%: H2O+TFA al 0,05% (caudal 1,3 ml/min), 40ºC
Gradiente:	5:95 (0 min) (5:95 (0,3 min) (95:5 (3,5 min) (95:5 (4 min)

Ionización: ESI+

Método E (=met. e):

Sistema: Waters: bomba 1525, 996 PDA, LCT classic TOF-MS

Columna: Waters XBridge C18; 4,6 x 50 mm; 2,5 □M

Eluyente: ACN + TFA al 0,05%: H2O+TFA al 0,05% (caudal 1,7 ml/min), 40ºC

Gradiente: 5:95 (0 min) (5:95 (0,2 min) (95:5 (2,4 min) (95:5 (3,2 min) (5:95 (3,3 min) (5:95 (4,0 min)

Ionización: ESI+

Método F (=met. f):

Sistema: Waters: bomba 1525, 996 PDA, LCT classic TOF-MS

Columna: YMCJ'shere, 33 x 2 mm, 4 µM

Eluyente: ACN + TFA al 0,05%: H_2O+TFA al 0,05% (caudal 1,3 ml/min)

Gradiente: 5:95 (0 min) → 5:95 (2,5 min) → 95:5 (3 min)

Ionización: ESI+

Las purificaciones por HPLC preparativa sobre gel de sílice de fase inversa (RP) se realizaron por los siguientes métodos:

Método A (=met. A):

Columna: Merck (Darmstadt, Deutschland) Purosphere® RP18 25 x 250 mm, 10 µm

Eluyente: ACN:H_2O+TFA al 0,05% (caudal 25 ml/min)

Gradiente: 10:90 (0 min) → 90:10 (40 min)

Método B (=met. b)

Columna: Merck Purosphere® RP18 25 x 250 mm, 10 µm

Eluyente: ACN:H_2O+TFA al 0,05% (caudal 25 ml/min)

Gradiente: 0:100 (0 min) → 0:100 (5 min) → 20:80 (20 min)

Método C (=met. c)

Columna: Agilent Prep-C18, 30 x 250 mm, 10 µm

Eluyente: ACN:H_2O+TFA al 0,05% (caudal 75 ml/min)

Gradiente: 10:90 (0 min) → 90:10 (12,5 min) → 90:10 (15 min) → 10:90

(15,5 min) → 10:90 (17,5 min)

Método D (=met. D):

Columna:	Merck (Darmstadt, Deutschland) Purosphere® RP18 25 x 250 mm, 10 µm
Eluyente:	ACN:H_2O+HCl conc. al 0,05% (caudal 25 ml/min)
Gradiente:	10:90 (0 min) → 90:10 (40 min)

Método E (=met. E)

Columna:	Merck Purosphere® RP18 25 x 250 mm, 10 µm
Eluyente:	ACN:H_2O+HCl al 0,05% (caudal 25 ml/min)
Gradiente:	0:100 (0 min) → 0:100 (5 min) → 20:80 (20 min)

Método F (=met. F)

Columna:	Agilent Prep-C18, 30 x 250 mm, 10 µm
Eluyente:	ACN:H_2O+TFA al 0,05% (caudal 75 ml/min)
Gradiente:	0:100 (0 min) → 0:100 (5 min) → 20:80 (20 min)

Las reacciones se realizaron en un aparato de reacción convencional tal como matraces de una sola boca o de múltiples bocas, que, a menos que se indique otra cosa, de acuerdo con la necesidad, tenían una capacidad de 5 ml a 2000 ml y, según se requirió, se equiparon con un tabique de goma, tapón, condensador, agitador u otro equipo. A menos que se mencione otra cosa, todas las reacciones se realizaron en una atmósfera de argón como gas protector y se agitaron con agitadores magnéticos. Las reacciones de microondas se realizaron en el Emrys Optimizer de Personal Chemistry en recipientes con una capacidad de 0,5 a 10 ml de acuerdo con las necesidades.

Disolventes tales como diclorometano, etanol, dimetilformamida, metanol, isopropanol y similares se adquirieron en forma de disolventes "secos" y también se usaron de esta manera en las reacciones, sin que se mencione explícitamente en cada caso.

Abreviaturas utilizadas:

abs.	absoluto (a)
ACN	acetonitrilo
Boc	butoxicarbonilo
Ej.	ejemplo

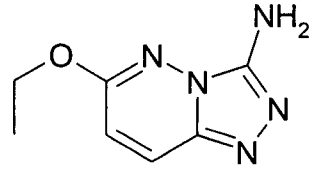
DCM	diclorometano
DIPEA	N,N-diisopropiletilamina (base de Hünig)
DMF	dimetilformamida
DMSO	dimetil sulfóxido
EA	acetato de etilo
equiv.	equivalentes
EtOH	etanol
h	hora(s)
HPLC	cromatografía líquida de alta resolución
Base de Hünig	N,N-diisopropil-N-etilamina
ta LC-MS	tiempo de retención del compuesto en la corriente de iones de la cromatografía líquida
LCUV/MS	cromatografía líquida ultravioleta/espectrometría de masas
NMP	1-metil-2-pirrolidona
MeOH	metanol
MtB éter	*tert*-butil metil éter
MO	microondas
RF	reflujo
TA	temperatura ambiente (de 20°Ca 25°C)
ta	tiempo de retención
TEA	trietilamina
TFA	ácido trifluoroacético
THF	tetrahidrofurano
TOTU	tetrafluoroborato de O-[(etoxicarbonil)cianometilenamino]-N,N,N',N'-tetrametiluronio

Síntesis de las unidades de la "mitad occidental":

W1

W1.001

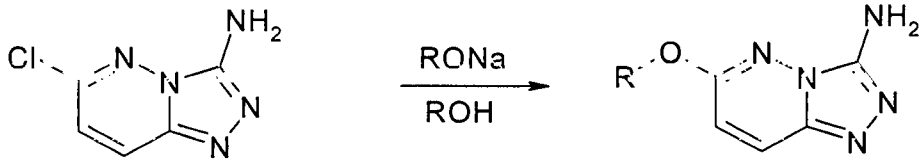
6-Etoxi-[1,2,4]triazolo[4,3-b]-piridazin-3-ilamina



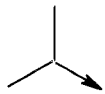
Se disolvió 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001a, 616 mg) en

etanol absoluto (40 ml) y se mezcló con porciones de etóxido sódico sólido (990 mg). Después de agitar a 55°Cdurante 2 h, se añadió agua y la fase acuosa se extrajo tres veces con diclorometano. Los extractos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 709 mg de producto en bruto del compuesto deseado con suficiente pureza. Tr de LC-MS: 0,51 min [M+H⁺]: 180,1 (met. b)

Los siguientes se sintetizaron de forma análoga:

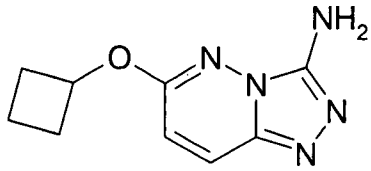


W2.001a

Número	R	Tr de LC-MS	[M+H⁺]	Comentario:
W1.002	metil-	022	166,1 (met. b)	W2.001a (100 mg); solución de metóxido sódico; producto: 95 mg
W1.003		0,69	194,1 (met. b)	W2.001a (100 mg); solución de isopropóxido sódico; producto: 84 mg

W1.004

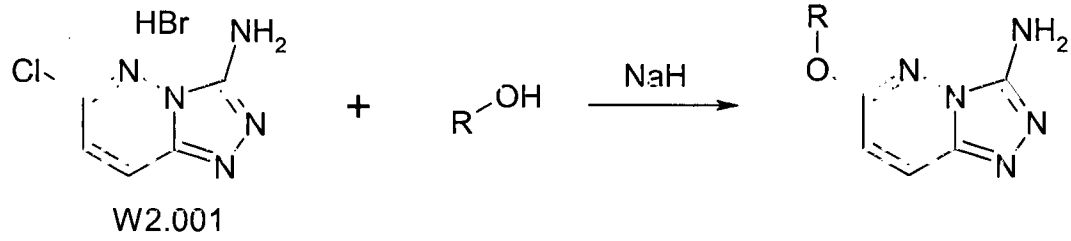
6-Ciclobutoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



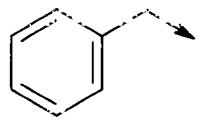
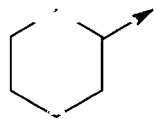
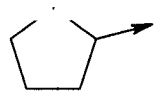
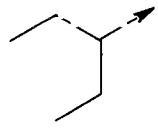
Se cargó inicialmente ciclobutanol (2,43 ml) a TA con agitación y se enfrió casi a 0°Coon un baño de hielo. Posteriormente, la mezcla se mezcló con porciones de hidruro sódico (146 mg). La suspensión formada se calentó a 55°Cdurante 30 min y se mezcló con porciones de hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001, 200 mg), suspendido en ciclobutanol (5 ml). Después de agitar a 55°Cdurante 1,5 h, la mezcla se dejó en reposo a TA durante una noche y después se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 136 mg del compuesto del título en forma sólida. Tr de LC-MS: 0,82 min [M+H⁺]: 206,2

(met. a)

Las siguientes unidades se sintetizaron de forma análoga:

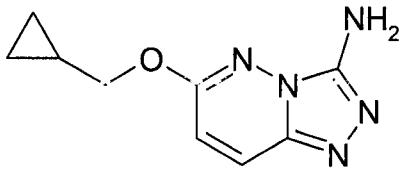


W2.001

Número	R	Tr de LC-MS	[M+H+]	Comentario:
W1.005		0,89 min	242,1 (met. a)	Se usó W2.001a (100 mg) disuelto en NMP; el producto en bruto se purificó por cromatografía usando gel de sílice con un gradiente de diclorometano/metanol; producto: 48 mg
W1.006		0,95 min	234,1 (met. a)	W2.001 (200 mg); el producto en bruto se purificó por HPLC preparativa (met. A); producto: 47 mg (sal TFA)
W1.007		0,88 min	220,1 (met. a)	W2.001 (463 mg); el producto en bruto se purificó por HPLC preparativa (met. A); producto: 15 mg (sal TFA)
W1.008		0,92 min	222,1 (met. a)	Se usó W2.001a (194 mg) suspendido en una mezcla de 10 ml de DMF y 5 ml de 3-pentanol; el producto en bruto se purificó por cromatografía usando gel de sílice con un gradiente de diclorometano/metanol; producto: 155 mg

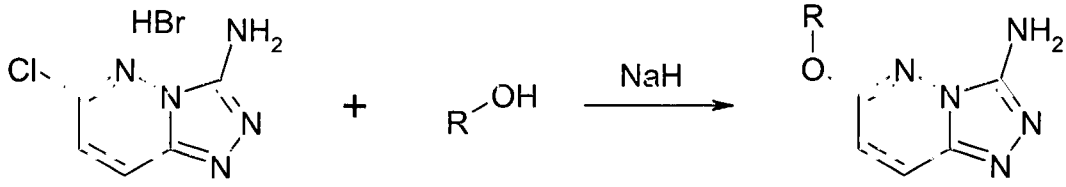
W1.009

6-Ciclopropilmetoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

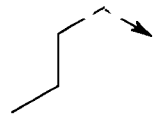
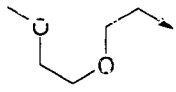


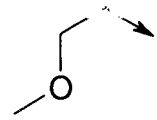
Se cargó inicialmente ciclopropilmetanol (2,64 ml) en DMF (35 ml), se mezcló en una atmósfera de argón con hidruro sódico (795 mg) y se agitó a 40°Cdurante 1 h. Posteriormente, se añadió gota a gota hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001; 1,66 g) disuelto en DMF (35 ml). Después de 1 h, la mezcla se mezcló con agua y se extrajo por agitación cuatro veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron por evaporación rotatoria. El residuo se trituró con MtB éter, se retiró por filtración con succión y se secó. Se obtuvieron 720 mg del compuesto del título. Tr de LC-MS: 0,80 min [M+H$^+$]: 206,1 (met. f)

Las siguientes unidades se sintetizaron de forma análoga:



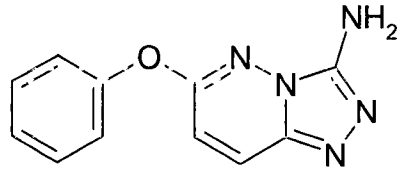
W2.001

Número	R	Tr de LC-MS [min]	[M+H$^+$]:	Comentario:
W1.010		0,91	208,2 (met. a)	W2.001 (1,75 g); se agitó a 45°Cdurante 1,5 h; producto: 820 mg
W1.011		0,63	254,1 (met. a)	W2.001 (2,5 g); el producto en bruto se purificó por medio de un cartucho de gel de sílice (120 g, gradiente; diclorometano al 0-20%/metanol en 60 min); producto: 1,08 g

W1.012		0,52	210,1 (met. a)	W2.001 (2,5 g); el producto en bruto se purificó por medio de un cartucho de gel de sílice (40 g, gradiente; diclorometano al 0-20%/metanol en 60 min); producto: 1,04 g

W1.013

6-Fenoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

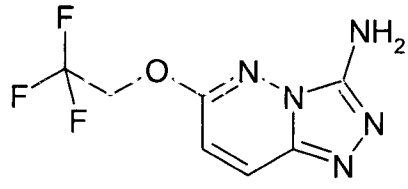


Inicialmente, se cargó hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001; 200 mg) disuelto en NMP (4 ml). Después, se introdujo fenóxido sódico (135 mg) a TA. Después de agitar a TA durante una hora, la reacción se completó con calentamiento a 55ºCdurante 2 h. Posteriormente, la mezcla se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. El producto en bruto se purificó usando gel de sílice con un gradiente de diclorometano/metanol. Se obtuvieron 38 mg del compuesto del título en forma sólida.

Tr de LC-MS: 0,80 min [M+H$^+$]: 228,1 (met. a)

W1.014

6-(2,2,2-Trifluoroetoxi)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

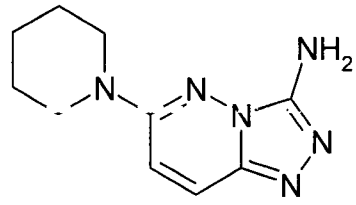


Se hicieron reaccionar 2,2,2-trifluoroetanol (1 ml), hidruro sódico (66 mg) e hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001, 100 mg) de acuerdo con W1.004, Se obtuvieron 87 mg del compuesto del título en forma sólida.

Tr de LC-MS: 0,68 min [M+H$^+$]: 234,1 (met. a)

W1.020

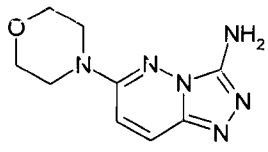
6-Piperidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Inicialmente, se cargó hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001; 100 mg) en agua (1 ml) y se mezcló con piperidina (260 µl) con agitación. Después, la mezcla se calentó a reflujo durante 1 h y, después de la refrigeración, se liberó del disolvente. Posteriormente, la mezcla se mezcló con agua y el sólido formado se retiró por filtración con succión y se secó. Las aguas madre se secaron y se mezclaron con un poco de agua. El sólido obtenido se retiró por filtración con succión y se secó. Después, el filtrado se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Las tres fracciones sólidas resultantes se combinaron y dieron lugar a 56 mg del compuesto del título.

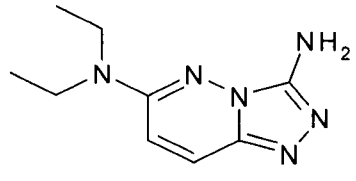
Tr de LC-MS: 0,77 min [M+H$^+$]: 219,1 (met. a)

Los siguientes se prepararon de manera análoga:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W1.021		0,55 min	221,1 (met. a)	W2.001 (150 mg); se calentó a reflujo durante 5 h; el producto seco en bruto se mezcló con agua y se extrajo directamente con DCM. Producto: 81 mg

W1.022

N*6*,N*6*-Dietil-[1,2,4]triazolo[4,3-b]piridazina-3,6-diamina

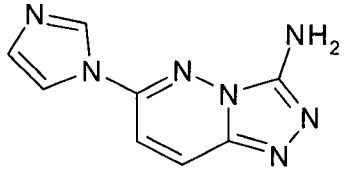


Inicialmente, se cargó hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001; 150 mg) en agua (5 ml) y se mezcló con dietilamina (814 µl) mientras se agitaba. Después, la mezcla se calentó a reflujo durante 16 h y después se añadió más cantidad de dietilamina (407 µl). Después de calentar a la temperatura de reflujo durante 12 h más, la mezcla se liberó del disolvente, se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 67 mg del compuesto del título.

Tr de LC-MS: 0,72 min [M+H$^+$]: 207,1 (met. a)

W1.023

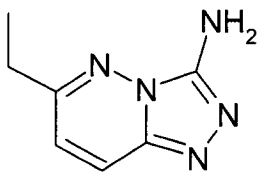
6-Imidazol-1-il-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Inicialmente, se cargó (6-imidazol-1-ilpiridazin-3-il)hidrazina (500 mg) en una mezcla de ácido acético (4 ml) y agua (8 ml) con la adición de acetato sódico (232 mg) a TA mientras se agitaba. Después, la mezcla se enfrió a 0°Cy se introdujo en porciones bromuro de cianógeno (330 mg). Después de agitar durante 2,5 h, la mezcla se dejó en reposo durante una noche. Después de enfriar a 0°C, la mezcla se hizo alcalina con una solución 10 M de hidróxido sódico y se extrajo repetidamente con EA. Las fases de EA combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 66 mg del compuesto del título. Aún estaba presente más cantidad de producto en la fase acuosa, que se liofilizó y se dejó en reposo. Tr de LC-MS: 1,46 min [M+H$^+$]: 202,1 (met. d)

W1.025

6-Etil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



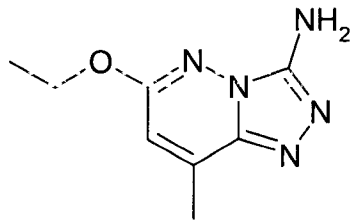
Inicialmente, se cargó hidrocloruro de (6-etilpiridazin-3-il)hidrazina (2 g) en una

mezcla de etanol (30 ml) y agua (6 ml) mientras se agitaba a TA. Después, se añadió cuidadosamente gota a gota bromuro de cianógeno (2,4 g disueltos en 7,5 ml de etanol y 1,5 ml de agua). Después de agitar a TA durante una hora, la mezcla se dejó en reposo durante una noche y, al día siguiente, se agitó durante 4 horas más. Después, el disolvente se retiró y el residuo se purificó por medio de HPLC preparativa (met. C). Las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida, se hicieron alcalinas con una solución saturada de carbonato potásico y se extrajeron repetidamente con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 830 mg del compuesto del título.

La fase acuosa de carbonato sódico se liofilizó de forma análoga, después se recogió con un poco de agua y se extrajo cinco veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 180 mg más del compuesto del título. Tr de LC-MS: 0,32 min [M+H$^+$]: 164,1 (met. a)

W1.030

6-Etoxi-3-metil-[1,2,4]triazolo[4,3-b]piridazin-8-ilamina



Se disolvió trifluoroacetato de 6-cloro-3-metil-[1,2,4]triazolo[4,3-b]piridazin-8-ilamina (W2.002b; 50 mg) en etanol (3,5 ml) mientras se agitaba a TA. Después, se añadió gota a gota etóxido sódico mientras se enfriaba con hielo (25 mg disueltos en 1,5 ml de etanol). Después de agitar a TA durante 2,5 h, la mezcla se calentó a 60°Cy, después de 2,5 h, se añadió un equivalente adicional de una solución de etóxido sódico. Después de dejar en reposo durante una noche, la mezcla se calentó de nuevo a 60°C, se añadieron dos equivalentes adicionales de una solución de etóxido sódico y la mezcla se agitó durante 4 h. Posteriormente, la mezcla se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 27 mg del compuesto del título.

Tr de LC-MS: 0,67 min [M+H$^+$]: 194,1 (met. a)

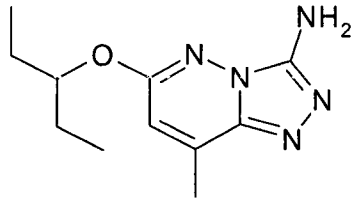
Alternativa:

Se disolvió hidrobromuro de 6-cloro-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.002; 2,5 g) en etanol (50 ml), se mezcló en una atmósfera de argón con etóxido sódico (3,86 g) y se agitó a 60°Cdurante 1 h. Después, la mezcla se secó y el residuo se purificó usando un cartucho de 40 g de gel de sílice (gradiente de diclorometano al 0-20%-etanol en 40 min). Las fracciones limpias del producto se combinaron y se secaron. Se obtuvieron 1,76 g del compuesto del título.

Tr de LC-MS: 1,48 min [M+H$^+$]: 194,1 (met. e)

W1.031

6-(1-Etilpropoxi)-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

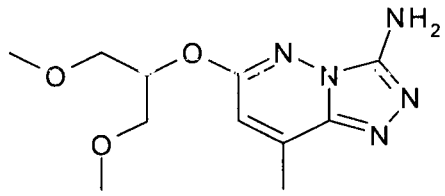


Se cargó inicialmente 3-pentanol (10,2 ml) a TA con agitación y se enfrió casi a 0°Ccon un baño de hielo. Posteriormente, la mezcla se mezcló con porciones de hidruro sódico (511 mg). La suspensión formada se calentó a 55°Cdurante 30 min y se mezcló con porciones de trifluoroacetato de 6-cloro-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.002b; 500 mg), suspendido en 3-pentanol (5 ml) y DMF (10 ml). Después de agitar a 55°Cdurante 1,5 h, la mezcla se dejó en reposo a TA durante una noche, la DMF se retiró a presión reducida y después el residuo se mezcló con agua y se extrajo cuatro veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. El residuo se purificó por medio de HPLC preparativa (met. A) y las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida, se hicieron alcalinas con una solución saturada de carbonato potásico y se extrajeron repetidamente con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 198 mg del compuesto del título.

Tr de LC-MS: 1,24 min [M+H$^+$]: 236,2 (met. a)

W1.032

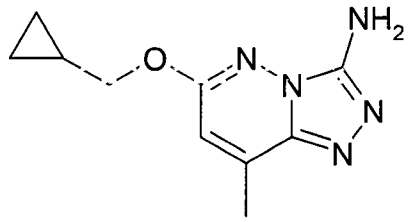
6-(2-Metoxi-1-metoximetiletoxi)-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se cargó inicialmente 1,3-dimetoxipropan-2-ol (12,96 ml) en DMF (25 ml), se mezcló en una atmósfera de argón con hidruro sódico (681 mg) y se agitó a 40°Cdurante 1 h. Posteriormente, se añadió gota a gota hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.002; 1,5 g), disuelto en DMF (25 ml) durante 20 min. Después de 1 h, la mezcla se mezcló con agua y se extrajo por agitación cuatro veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron por evaporación rotatoria. El residuo se trituró con MtB éter, se retiró por filtración con succión y se secó. Se obtuvieron 764 mg del compuesto del título. Tr de LC-MS: 0,74 min [M+H$^+$]: 268,1 (met. a)

W1.033

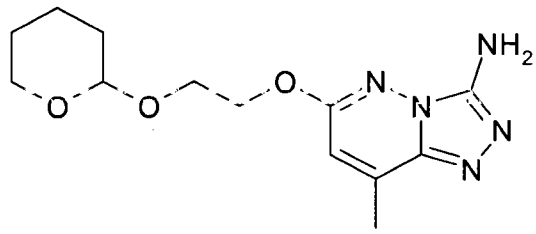
6-Ciclopropilmetoxi-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se cargó inicialmente ciclopropilmetanol (2,99 ml) en DMF (30 ml), se mezcló en una atmósfera de argón con hidruro sódico (907 mg) y se agitó a 50°Cdurante 1 h. Posteriormente, se disolvió hidrobromuro de 6-cloro-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.002; 2,0 g) en DMF (30 ml) y se añadió un equivalente de la solución de alcóxido. Después de agitar a 50°Cdurante una hora, se añadieron dos equivalentes adicionales de una solución de alcóxido y la mezcla se agitó adicionalmente a 50°C. Después, la mezcla de reacción se secó y se purificó usando gel de sílice (cartucho de 80 g, gradiente de diclorometano/metanol de 0-10% en 40 min). Se obtuvieron 620 mg del compuesto del título. Tr de LC-MS: 0,57 min [M+H$^+$]: 220,1 (met. b)

W1.034

8-Metil-6-[2-(tetrahidropiran-2-iloxi)etoxi]-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

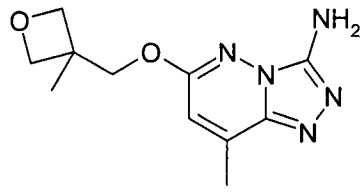


Se cargó inicialmente 2-(tetrahidropiran-2-iloxi)etanol (3,35 ml) en DMF (25 ml), se mezcló en una atmósfera de argón con hidruro sódico (681 mg) y se agitó a 40°Cdurante 0,5 h. Posteriormente, se añadió gota a gota hidrobromuro de 6-cloro-3-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.002; 1,5 g), disuelto en DMF (25 ml). Después de 40 min, la mezcla se mezcló con agua y se extrajo por agitación cuatro veces con diclorometano. Para eliminar el exceso de alcohol, la mezcla se cromatografió primero a través de una columna corta de gel de sílice con MtB éter y después con 8:2 de diclorometano/metanol. Las fracciones limpias del producto se combinaron y se secaron. Se obtuvieron 678 mg del compuesto del título.

Tr de LC-MS: 0,88 min [M+H$^+$]: 294,1 (met. a)

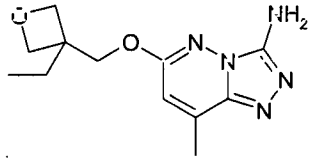
W1.035

3-Metil-6-(3-metiloxetan-3-ilmetoxi)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



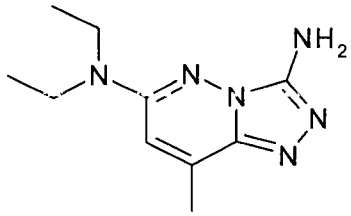
Se cargó inicialmente (3-metiloxetan-3-il)metanol (1,74 g) en DMF (30 ml), se mezcló en una atmósfera de argón con hidruro sódico (408 mg) y se agitó a 45°Cdurante 0,5 h. Posteriormente, se disolvió hidrobromuro de 6-cloro-3-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.002; 1,5 g) en DMF (30 ml) y se añadió un equivalente de la solución de alcóxido (10 ml). Después de agitar a 45°Cdurante 30 min, se añadieron 0,5 equivalentes más de una solución de alcóxido, seguido de 0,5 equiv., cada uno después de 30 y 60 min más. Después, la mezcla se mezcló con agua y la mezcla de reacción se secó y se purificó usando gel de sílice (cartucho de 80 g, gradiente de diclorometano/metanol de 0-20% en 60 min). Se obtuvieron 758 mg del compuesto del título. Tr de LC-MS: 0,49 min [M+H$^+$]: 250,1 (met. b)

Los siguientes se prepararon de manera análoga:

Número		Tr de LC-MS	[M+H⁺]:	Comentario:
W1.036		0,57 min	264,1 (met. b)	W2.002 (1 g); producto: 550 mg

W1.040

N*6*,N*6*-Dietil-8-metil-[1,2,4]triazolo[4,3-b]piridazina-3,6-diamina

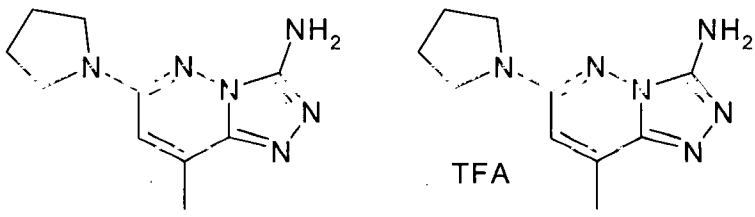


Se disolvió hidrobromuro de 6-cloro-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.002; 250 mg) en DMF abs. (2 ml) y se mezcló con dietilamina (7 ml). Después, la mezcla de reacción se puso en un bloque de calentamiento a 80°Coon agitación durante 11 días. Después, el disolvente se retiró y el residuo se mezcló con un poco de agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. El residuo se purificó por medio de HPLC preparativa (met. A) y las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida, se hicieron alcalinas con una solución saturada de carbonato potásico y se extrajeron repetidamente con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 100 mg del compuesto del título.

Tr de LC-MS: 0,70 min [M+H⁺]: 221,2 (met. b)

W1.041 y W1.041a

8-Metil-6-pirrolidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina y trifluoroacetato de 8-metil-6-pirrolidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



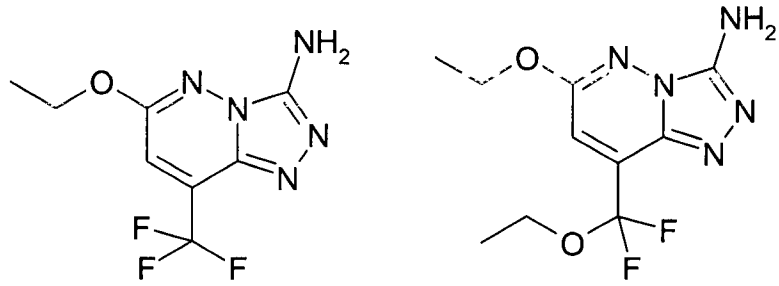
Se disolvió hidrobromuro de 6-cloro-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.002; 250 mg) en DMF abs. (2 ml) y se mezcló con pirrolidina (2 ml). Después, la mezcla de reacción se puso en el bloque de calentamiento a 80°Con agitación durante 1,5 h. Posteriormente, el disolvente se retiró y el residuo se mezcló con un poco de agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Cuando el residuo se disolvió en acetonitrilo/agua + TFA al 0,05%, precipitó un sólido, que se retiró por filtración con succión y se secó. Se obtuvieron 40 mg de 8-metil-6-pirrolidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina. Las aguas madre se purificaron por medio de HPLC preparativa (met. A), y las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida y se liofilizaron. Se obtuvieron 11 mg de 8-metil-6-pirrolidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina en forma de la sal del ácido trifluoroacético.

8-Metil-6-pirrolidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

Tr de LC-MS: 0,76 min [M+H$^+$]: 219,1 (met. b)

W1.045 y W1.046

6-Etoxi-8-trifluorometil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina y 6-etoxi-8-(etoxidifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se cargó inicialmente 6-cloro-8-trifluorometil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.004; 65 mg) en etanol (6 ml) y se mezcló con etóxido sódico (21 mg). La mezcla de reacción se agitó a 50°Cdurante 4 h. Después de un periodo de refrigeración, la mezcla se mezcló con agua y se concentró. El residuo se recogió en acetato de etilo y se lavó tres veces con agua. La fase de acetato de etilo se secó con sulfato sódico, se filtró y se concentró. El producto en bruto se purificó por medio de HPLC preparativa (met. E). Las fracciones que contenían el producto, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo, se ajustaron a un valor de pH de 9 con hidrogenocarbonato sódico y se extrajeron tres veces con acetato de etilo. Los extractos orgánicos combinados se secaron sobre carbonato

sódico, se filtraron y se concentraron. Se obtuvieron 15 mg de 6-etoxi-8-trifluorometil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina y 23 mg de 6-etoxi-8-(etoxidifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina.

6-Etoxi-8-trifluorometil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina, W1.045

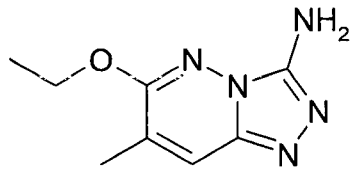
Tr de LC-MS: 0,70 min [M+H$^+$]: 248,1 (met. b)

6-Etoxi-8-(etoxidifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina, W1.046

Tr de LC-MS: 0,82 min [M+H$^+$]: 272,2 (met. b)

W1.050

6-Etoxi-7-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

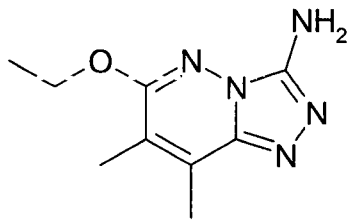


Se disolvió 6-cloro-7-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.005; 1 g) en etanol (50 ml), se mezcló en una atmósfera de argón con etóxido sódico (2,2 g) y se agitó a 60°Cdurante 1 h. Después, la mezcla se secó y el residuo se purificó usando un cartucho de 40 g de gel de sílice (gradiente de diclorometano al 0-20%-etanol en 40 min). Las fracciones limpias del producto se combinaron y se secaron. Se obtuvieron 480 mg del compuesto del título.

Tr de LC-MS: 2,07 [M+H$^+$]: 194,1 (met. d)

W1.055

6-Etoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



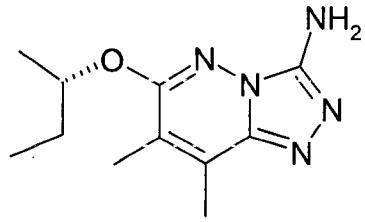
Se disolvió hidrobromuro de 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006; 4 g) en etanol (120 ml), se mezcló en una atmósfera de argón con etóxido sódico (5,86 g) y se agitó a 60°Cdurante 1 h. Después, la mezcla se secó y el residuo se purificó usando un cartucho de 40 g de gel de sílice (gradiente de

diclorometano al 0-20%-etanol en 40 min). Las fracciones limpias del producto se combinaron y se secaron. Se obtuvieron 3,24 g del compuesto del título, que aún contenía cantidades residuales de diclorometano.

Tr de LC-MS: 0,53 min [M+H$^+$]: 208,1 (met. b)

W1.056

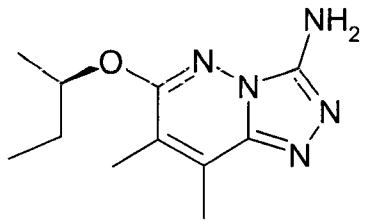
6-((S)-sec-Butoxi)-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se cargó inicialmente (S)-butan-2-ol (1,7 ml) a TA con agitación y se enfrió casi a 0°Con un baño de hielo. Posteriormente, la mezcla se mezcló con porciones de hidruro sódico (85 mg). La suspensión formada se calentó a 55°Cdurante 1,5 h y después se mezcló con porciones de 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006a, 100 mg), suspendida en (S)-butan-2-ol (2 ml) y DMF (2 ml). Después de agitar a 55°Cdurante 1 h, la mezcla se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se aislaron 105 mg del compuesto del título con suficiente pureza. Tr de LC-MS: 0,81 min [M+H$^+$]: 236,2 (met. b)

W1.057

6-((R)-sec-Butoxi)-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

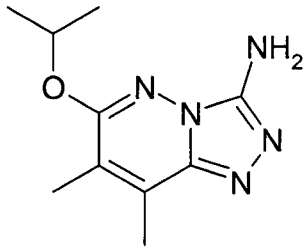


Se desprotonó (R)-butan-2-ol (0,5 ml) de forma análoga a W1.056 con hidruro sódico (85 mg), se hizo reaccionar con 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006a, 100 mg), suspendida en DMF (2 ml), y se sometió a tratamiento. Se aislaron 75 mg del compuesto del título con suficiente pureza.

Tr de LC-MS: 0,81 min [M+H$^+$]: 236,2 (met. b)

W1.058

6-Isopropoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

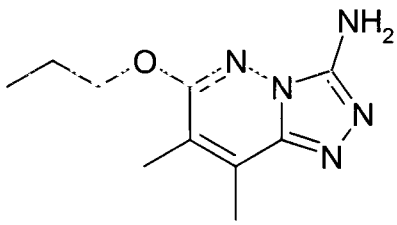


Se desprotonó isopropanol (27 ml) de forma análoga a W1.056 con hidruro sódico (1,3 g), se hizo reaccionar con 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006a, 1 g), disuelta en isopropanol (10 ml) y DMF (10 ml), y se sometió a tratamiento. Se aislaron 647 mg del compuesto del título con suficiente pureza.

Tr de LC-MS: 0,74 min [M+H$^+$]: 222,2 (met. b)

W1.059

7,8-Dimetil-6-propoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

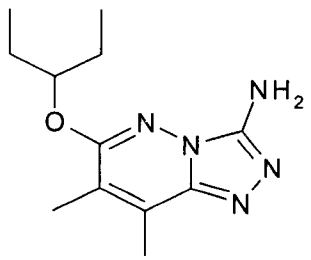


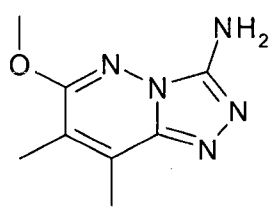
Se desprotonó 1-propanol (28 ml) de forma análoga a W1.056 con hidruro sódico (1,3 g), se hizo reaccionar con 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006a, 1 g), disuelta en 1-propanol (10 ml) y DMF (10 ml), y se sometió a tratamiento. Se aislaron 647 mg del compuesto del título con suficiente pureza.

Tr de LC-MS: 0,75 min [M+H$^+$]: 222,2 (met. b)

W1.060 y W1.061

6-(1-Etilpropoxi)-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina y 6-metoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



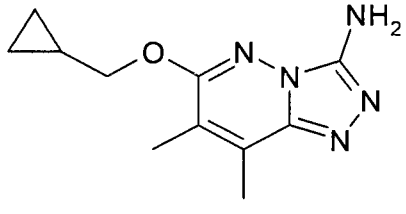


Se cargó inicialmente 3-pentanol (1,5 ml) a TA con agitación y se enfrió casi a 0ºCcon un baño de hielo. Posteriormente, la mezcla se mezcló con porciones de hidruro sódico (117 mg). La suspensión formada se calentó a 55ºCdurante 1,5 h y después se mezcló con porciones de 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006a, 100 mg), suspendida en 3-pentanol (1 ml) y DMF (1,5 ml). Después de agitar a 55ºCdurante 2 h, la mezcla se dejó en reposo a TA durante una noche, se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. El residuo se purificó por medio de HPLC preparativa (met. A) y las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida, se hicieron alcalinas con una solución saturada de carbonato potásico y se extrajeron repetidamente con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 79 mg de 6-(1-etilpropoxi)-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina y 10 mg de 6-metoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina, que se formaron en la mezcla de reacción como resultado de la contaminación con metanol.

6-(1-Etilpropoxi)-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina, W1.060
Tr de LC-MS: 1,30 min [M+H$^+$]: 250,2 (met. a)

6-Metoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina, W1.061
Tr de LC-MS: 0,88 min [M+H$^+$]: 194,1 (met. a)

W1.062
6-Ciclopropilmetoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

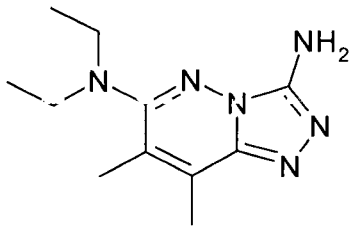


Se cargó inicialmente ciclopropilmetanol (2,64 ml) en DMF (20 ml), se mezcló en una atmósfera de argón con hidruro sódico (862 mg) y se agitó a 50ºCdurante 1 h. Posteriormente, se añadieron hidrobromuro de 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006, 2 g), disuelto en DMF (20 ml), y un equivalente de la solución de alcóxido. Después de agitar a 50ºCdurante una hora, se añadieron dos

equivalentes adicionales de una solución de alcóxido y la mezcla se agitó adicionalmente a 50°C. Después, la mezcla de reacción se secó y se purificó usando gel de sílice (cartucho de 40 g, gradiente de diclorometano/metanol de 0-10% en 40 min). Se obtuvieron 625 mg del compuesto del título. Tr de LC-MS: 0,62 min [M+H$^+$]: 234,1 (met. b)

W1.065

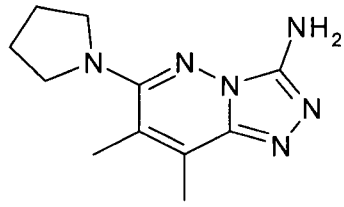
N*6*,N*6*-Dietil-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazina-3,6-diamina



Se cargaron inicialmente dos porciones de 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006a, 300 mg y 650 mg divididos entre 2 recipientes para microondas), cada una disuelta en 12 ml de dietilamina y se mezclaron con hexafluorofosfato de 1-butil-3-metilimidazolio (150 µl). Posteriormente, se pusieron en el microondas a 180°Cdurante 4 h. Con el fin de completar la reacción, se pusieron de nuevo en el microondas a 180°Cdurante 4 h y después se dejaron en reposo durante una noche. Las dos mezclas de reacción se combinaron en un matraz de fondo redondo y se secaron. El residuo se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. El residuo se purificó por medio de HPLC preparativa (met. F) y las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida, se hicieron alcalinas con una solución saturada de carbonato potásico y se extrajeron repetidamente con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 900 mg del compuesto del título. Tr de LC-MS: 0,77 min [M+H$^+$]: 235,2 (met. b)

W1.066

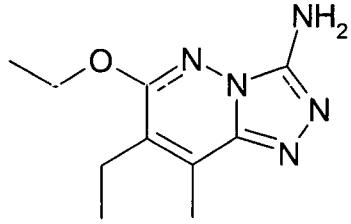
7,8-Dimetil-6-pirrolidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se cargó inicialmente 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006a, 500 mg) en pirrolidina (5 ml) a TA mientras se agitaba. Después, la mezcla se calentó a 65°Cdurante 4 h. Después, la pirrolidina se retiró y el residuo se recogió con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 438 mg del compuesto del título. Tr de LC-MS: 0,72 min [M+H$^+$]: 233,2 (met. b)

W1.070

6-Etoxi-7-etil-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

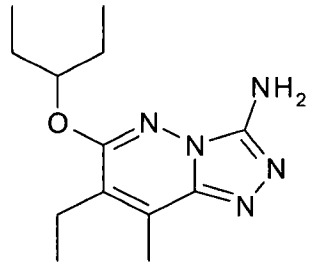


Se cargó inicialmente 6-cloro-7-etil-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.007; 380 mg) en etanol (45 ml) a TA mientras se agitaba, se mezcló con etóxido sódico (244 mg) y se calentó a 55°Cdurante 3 h. Después, se añadió un equivalente adicional de etóxido sódico y la mezcla se agitó una vez más a 55°C durante 3 h. Después de dejarla en reposo durante el fin de semana, la mezcla se secó y el residuo se recogió con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 387 mg del compuesto del título.

Tr de LC-MS: 0,76 min [M+H$^+$]: 222,2 (met. b)

W1.071

7-Etil-6-(1-etilpropoxi)-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

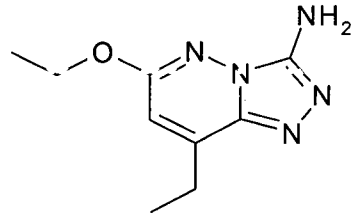


Se cargó inicialmente 3-pentanol (2,5 ml) a TA con agitación. Después, se añadió hidruro sódico (91 mg) mientras se enfriaba con hielo. Después de agitar a 55°Cdurante 2,5 h, se añadió gota a gota 6-cloro-7-etil-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.007; 120 mg), disuelta en 3-pentanol (2 ml) y DMF (4 ml). Después de agitar durante 1 h, la mezcla se dejó en reposo a TA durante una noche y la mezcla de reacción se mezcló con agua y diclorometano y después se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 126 mg del compuesto del título.

Tr de LC-MS: 0,90 min [M+H$^+$]: 264,2 (met. b)

W1.075

6-Etoxi-8-etil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

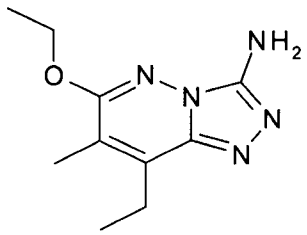


Se disolvió 6-cloro-8-etil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.003; 700 mg) en etanol (100 ml) mientras se agitaba. Después, la mezcla de reacción se mezcló con etóxido sódico (724 mg) y se agitó a TA durante 2 h. Posteriormente, la mezcla se calentó a 45°Cdurante 3 h. Después de que se retirara el disolvente, el residuo se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 670 mg del compuesto del título.

Tr de LC-MS: 0,64 min [M+H$^+$]: 208,2 (met. b)

W1.076

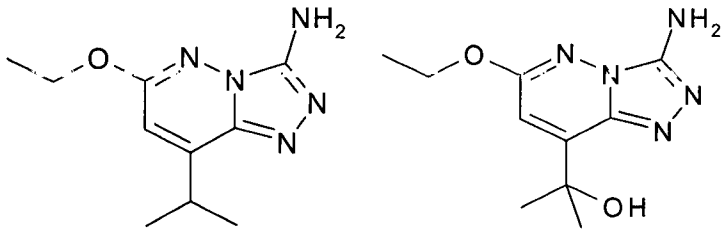
6-Etoxi-8-etil-7-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se disolvió 6-cloro-3-etil-7-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.008, 273 mg) en etanol abs. (20 ml) mientras se agitaba. Después, la mezcla de reacción se mezcló con etóxido sódico (176 mg) y se agitó a TA durante 3,5 h. Después de dejar en reposo durante el fin de semana, el disolvente se retiró y el residuo se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 230 mg del compuesto del título. Tr de LC-MS: 0,75 min [M+H$^+$]: 222,2 (met. b)

W1.080 y W1.081

6-Etoxi-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina y 2-(3-amino-6-etoxi-[1,2,4]triazolo[4,3-b]piridazin-8-il)propan-2-ol



Se cargó inicialmente 6-cloro-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.009, 77 mg) en etanol (8 ml) mientras se agitaba a TA y se mezcló con etóxido sódico (50 mg). Después de agitar durante 4,5 h, la mezcla se dejó en reposo durante una noche y después el disolvente se retiró. El residuo se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 52 mg de los compuestos del título en forma de una mezcla (de acuerdo con ^{1}H RMN, ~70:30 en favor de 6-etoxi-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina).

6-Etoxi-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina, W1.080

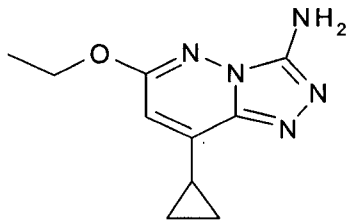
Tr de LC-MS: 0,76 min [M+H$^+$]: 222,2 (met. b)

2-(3-Amino-6-etoxi-[1,2,4]triazolo[4,3-b]piridazin-8-il)propan-2-ol, W1.081

Tr de LC-MS: 0,40 min [M+H$^+$]: 238,1 (met. b)

W1.082

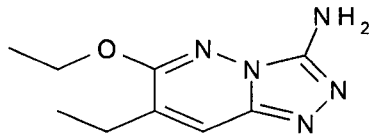
8-Ciclopropil-6-etoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se cargó inicialmente 6-cloro-8-ciclopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.010, 77 mg) en etanol (10 ml) mientras se agitaba a TA y se mezcló con etóxido sódico (67 mg). Después de agitar durante 4,5 h, la mezcla se dejó en reposo durante una noche y después el disolvente se retiró. El residuo se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 91 mg del compuesto del título. Tr de LC-MS: 0,71 min [M+H$^+$]: 220,2 (met. b)

W1.085

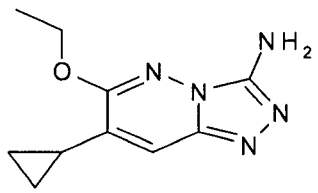
6-Etoxi-7-etil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se hizo reaccionar sal trifluoroacetato de 6-cloro-7-etil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.011, 82 mg) y se trató de forma análoga a W1.075. Se obtuvieron 77 mg del compuesto del título. Tr de LC-MS: 0,69 min [M+H$^+$]: 208,2 (met. b)

W1.086

7-Ciclopropil-6-etoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

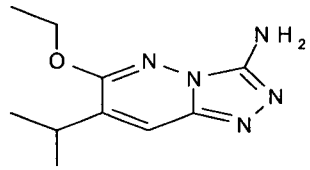


Se hizo reaccionar 6-cloro-7-ciclopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

(W2.012, 30 mg) y se trató de forma análoga a W1.075. Se obtuvieron 31 mg del compuesto del título. Tr de LC-MS: 0,70 min [M+H$^+$]: 220,2 (met. b)

W1.087

6-Etoxi-7-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

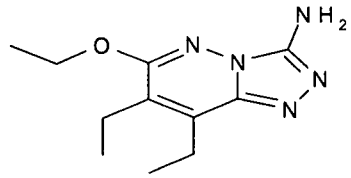


Se hizo reaccionar 6-cloro-7-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.013, 30 mg) y se trató de forma análoga a W1.075. Se obtuvieron 31 mg del compuesto del título.

Tr de LC-MS: 0,76 min [M+H$^+$]: 222,2 (met. b)

W1.090

6-Etoxi-7,8-dietil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

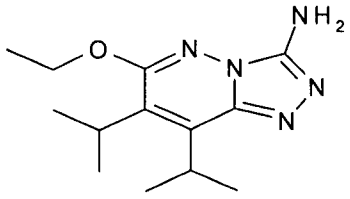


Se disolvió 6-cloro-7,8-dietil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.014, 0,1 g) en etanol (13 ml) mientras se agitaba y permanecía en una atmósfera de argón. Después, la mezcla de reacción se mezcló con etóxido sódico (61 mg), se agitó a TA durante 1 h y después a 55°Cdurante 30 min. Posteriormente, se añadieron 2 equivalentes más de etóxido sódico y la mezcla se agitó a 55°Cdurante 4,5 h. Después de que se añadiera 1 equivalente más de etóxido sódico, la mezcla se agitó a 55°Cdurante 2,5 h y se dejó en reposo durante el fin de semana. Después, el disolvente se retiró y el residuo se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 92 mg del compuesto del título.

Tr de LC-MS: 0,80 min [M+H$^+$]: 236,2 (met. b)

W1.091

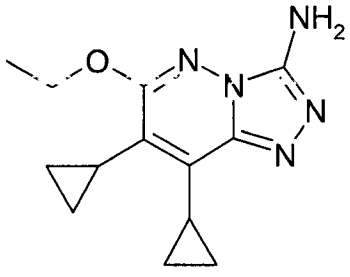
6-Etoxi-7,8-diisopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se disolvió 6-cloro-7,8-diisopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.015, 0,1 g) en etanol (15 ml) mientras se agitaba y permanecía en una atmósfera de argón. Después, la mezcla de reacción se mezcló con etóxido sódico (110 mg), se agitó a TA durante 1 h y después a 55ºCdurante 1 h. Posteriormente, la mezcla se dejó en reposo durante una noche y se agitó de nuevo a 55ºCdurante 7,5 h. Después, el disolvente se retiró y el residuo se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 100 mg del compuesto del título. Tr de LC-MS: 0,90 min [M+H$^+$]: 264,2 (met. b)

W1.092

7,8-Diciclopropil-6-etoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

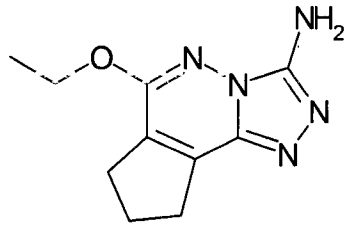


Se disolvió 6-cloro-7,8-diciclopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.016, 0,1 g) en etanol (20 ml) mientras se agitaba y permanecía en una atmósfera de argón. Después, la mezcla de reacción se mezcló con etóxido sódico (110 mg), se agitó a TA durante 1 h y después a 55ºCdurante 1 h. Posteriormente, la mezcla se dejó en reposo durante una noche y después se calentó a reflujo durante 7,5 h. Después de dejar en reposo durante el fin de semana, el disolvente se retiró y el residuo se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 100 mg del compuesto del título.

Tr de LC-MS: 0,84 min [M+H$^+$]: 260,2 (met. b)

W1.095

6-Etoxi-8,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-3-ilamina

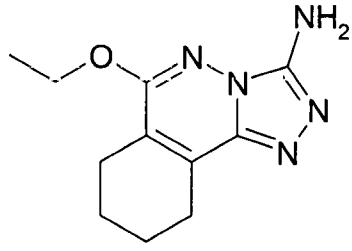


Se disolvió hidrobromuro de 6-cloro-8,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.017, 1,0 g) en etanol abs. (50 ml) mientras se agitaba y permanecía en una atmósfera de argón. Después, la mezcla de reacción se mezcló con etóxido sódico (1,41 g) y se agitó a 60°Cdurante 1 h. Después de que se retirara el disolvente, el residuo se purificó usando un cartucho de 40 g de gel de sílice (gradiente 0-20% de diclorometano-etanol en 60 min). Las fracciones limpias del producto se combinaron y se secaron. Se obtuvieron 662 mg del compuesto del título.

Tr de LC-MS: 0,56 [M+H$^+$]: 220,1 (met. b)

W1.096

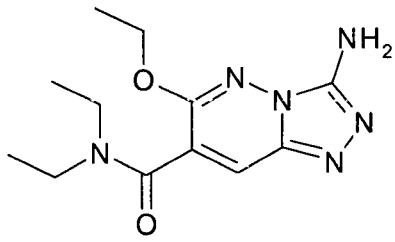
6-Etoxi-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]ftalazin-3-ilamina



Se disolvió 6-cloro-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]ftalazin-3-ilamina (W2.018, 1,0 g) en etanol (50 ml) mientras se agitaba y permanecía en una atmósfera de argón. Después, la mezcla de reacción se mezcló con etóxido sódico (1,34 g) y se agitó a 60°Cdurante 1 h. Después de que se retirara el disolvente, el residuo se purificó usando un cartucho de 40 g de gel de sílice (gradiente de 0.20% de diclorometano-etanol en 40 min). Las fracciones limpias del producto se combinaron y se secaron. Se obtuvieron 491 mg del compuesto del título. Tr de LC-MS: 0,95 [M+H$^+$]: 234,1 (met. a)

W1.100

N,N-Dietil-3-amino-6-etoxi-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida

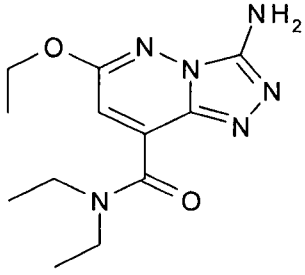


Se cargó inicialmente N,N-dietil-3-amino-6-cloro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida (W2.019, 50 mg) en etanol (5 ml) y se mezcló con etóxido sódico (28 mg) mientras se agitaba. Después de agitar durante 7 h a TA y dejar en reposo durante una noche, el disolvente se retiró y la mezcla se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 51 mg del compuesto del título.

Tr de LC-MS: 1,00 min [M+H$^+$]: 279,2 (met. b)

W1.101

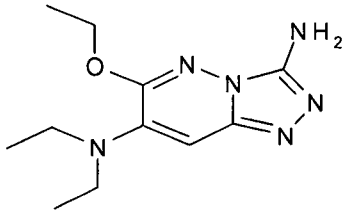
N,N-Dietil-3-amino-6-etoxi-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida



Se preparó N,N-dietil-3-amino-6-cloro-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida (W2.020, 50 mg) de forma análoga a W1.100. Se obtuvieron 51 mg del compuesto del título. Tr de LC-MS: 1,04 min [M+H$^+$]: 279,2 (met. b)

W1.102

6-Etoxi-N*7*,N*7*-dietil-[1,2,4]triazolo[4,3-b]piridazina-3,7-diamina

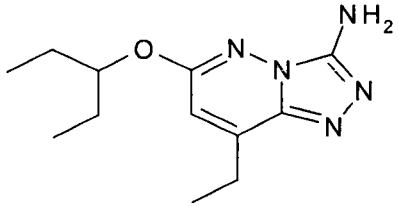


Se cargó inicialmente 6-cloro-N*7*,N*7*-dietil-[1,2,4]triazolo[4,3-b]piridazina-3,7-diamina (W2.021, 33 mg) en etanol (7 ml) y se mezcló con etóxido sódico (24 mg).

La mezcla de reacción se agitó a TA durante 4 h. Después, se agitó a 45°Cdurante 2 h más. Posteriormente, la mezcla se secó, el residuo se mezcló con agua y se extrajo tres veces con EA y fases de EA combinadas se secaron con sulfato de magnesio, se filtraron y se concentraron. Se obtuvieron 30 mg del compuesto del título en forma un producto en bruto, que estaba lo suficientemente limpio para la siguiente reacción. Tr de LC-MS: 1,13 min [M+H$^+$]: 251,2 (met. a)

W1.105

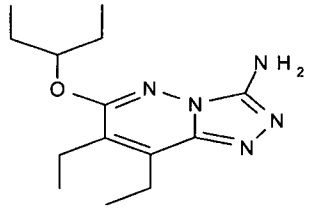
8-Etil-6-(1-etilpropoxi)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se cargó inicialmente 3-pentanol (1,2 ml) a TA con agitación. Después, se añadió hidruro sódico (77 mg) mientras se enfriaba con hielo. Después de agitar a 55°Cdurante 2,5 h, se añadió gota a gota 6-cloro-8-etil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.003, 60 mg), disuelta en 3-pentanol (1,5 ml) y DMF (4 ml). Después de agitar durante 2 h, la mezcla de reacción se dejó en reposo a TA durante una noche, se mezcló con agua y diclorometano y después se extrajo tres veces más con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 70 mg del compuesto del título. Tr de LC-MS: 0,87 min [M+H$^+$]: 250,2 (met. b)

W1.106

7,8-Dietil-6-(1-etilpropoxi)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

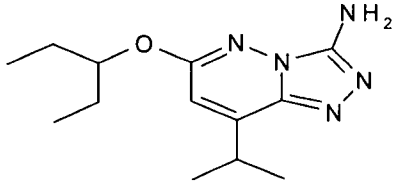


Se hizo reaccionar 6-cloro-7,8-dietil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.014, 100 mg) y se trató de forma análoga a W1.075. Se obtuvieron 110 mg del compuesto del título.

Tr de LC-MS: 0,93 min [M+H$^+$]: 278,2 (met. b)

W1.107

6-(1-Etilpropoxi)-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

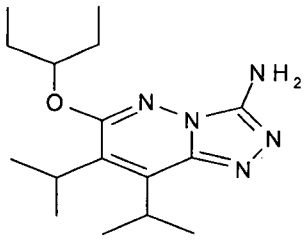


Se hizo reaccionar 6-cloro-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.009, 80 mg) y se trató de forma análoga a W1.075. Después, el producto en bruto se purificó por medio de HPLC preparativa (met. A) y las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida, se hicieron alcalinas con una solución saturada de carbonato potásico y se extrajeron repetidamente con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 51 mg del compuesto del título.

Tr de LC-MS: 0,91 min [M+H$^+$]: 264,2 (met. b)

W1.108

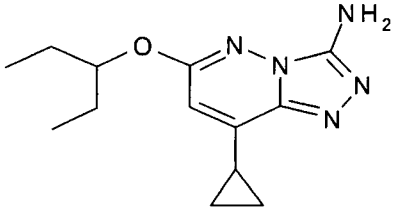
6-(1-Etilpropoxi)-7,8-diisopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se hizo reaccionar 6-cloro-7,8-diisopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.015, 100 mg), se trató y se purificó de forma análoga a W1.107. Se obtuvieron 72 mg del compuesto del título. Tr de LC-MS: 1,01 min [M+H$^+$]: 306,3 (met. b)

W1.109

8-Ciclopropil-6-(1-etilpropoxi)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

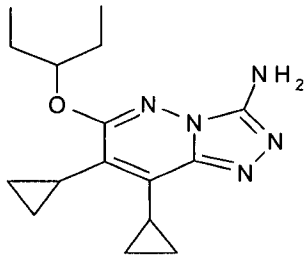


Se hizo reaccionar 6-cloro-8-ciclopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

(W2.010, 100 mg), se trató y se purificó de forma análoga a W1.107. Se obtuvieron 74 mg del compuesto del título. Tr de LC-MS: 0,89 min [M+H$^+$]: 262,2 (met. b)

W1.110

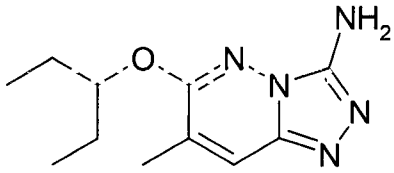
7,8-Diciclopropil-6-(1-etilpropoxi)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se hizo reaccionar 6-cloro-7,8-diciclopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.016, 100 mg), se trató y se purificó de forma análoga a W1.107. Se obtuvieron 35 mg del compuesto del título. Tr de LC-MS: 0,95 min [M+H$^+$]: 302,2 (met. b)

W1.111

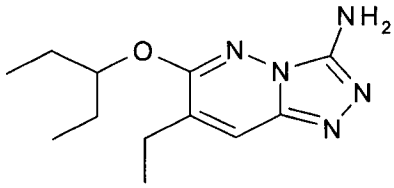
6-(1-Etilpropoxi)-7-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se cargó inicialmente 3-pentanol (30 ml) en una atmósfera de argón, se mezcló con hidruro sódico (1,48 g) y se agitó a 50°Cdurante 1 h. Posteriormente, se añadió lentamente gota a gota 6-cloro-7-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.005, 1,88 g), disuelta en 3-pentanol (130 ml) y DMF (60 ml), durante 1 h. Después de agitar durante 1 h, la mezcla se concentró y el residuo se mezcló con agua y se extrajo cuatro veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó usando un cartucho de 80 g de gel de sílice (gradiente de 0,10% de diclorometano-metanol en 40 min). Las fracciones limpias del producto se combinaron y se secaron. Se obtuvieron 1,25 g del compuesto del título. Tr de LC-MS: 2,60 min [M+H$^+$]: 236,1 (met. e)

W1.112

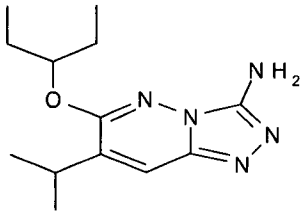
7-Etil-6-(1-etilpropoxi)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se hizo reaccionar 6-cloro-7-etil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.011, 150 mg), se trató y se purificó de forma análoga a W1.107. Se obtuvieron 103 mg del compuesto del título. Tr de LC-MS: 0,87 min [M+H$^+$]: 250,2 (met. b)

W1.113

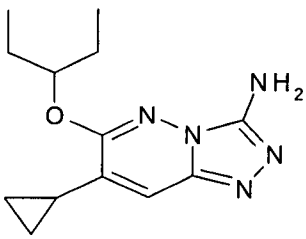
6-(1-Etilpropoxi)-7-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se hizo reaccionar 6-cloro-7-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.013, 100 mg) y se trató de forma análoga a W1.071. Se obtuvieron 132 mg del compuesto del título, que aún estaba contaminado con un poco de DMF. Tr de LC-MS: 0,90 min [M+H$^+$]: 264,2 (met. b)

W1.114

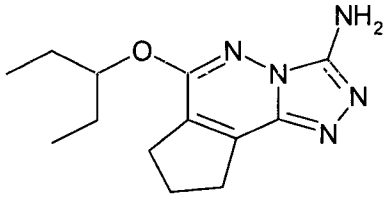
7-Ciclopropil-6-(1-etilpropoxi)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se hizo reaccionar 6-cloro-7-ciclopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.012, 100 mg) y se trató de forma análoga a W1.071. Se obtuvieron 116 mg del compuesto del título. Tr de LC-MS: 0,87 min [M+H$^+$]: 262,2 (met. b)

W1.115

6-(1-Etilpropoxi)-8,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-3-ilamina

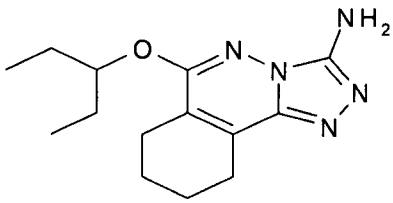


Se cargó inicialmente 3-pentanol (20 ml) en una atmósfera de argón, se mezcló con hidruro sódico (991 mg) y se agitó a 50°Cdurante 1 h. Posteriormente, se añadió lentamente gota a gota hidrobromuro de 6-cloro-8,9-dihidro-7H-ciclopenta[d][1,2,4]-triazolo[4,3-b]piridazin-3-ilamina (W2.017, 2,0 g), disuelto en 3-pentanol (20 ml) y DMF (100 ml), durante 1 h. Después de agitar durante 1 h, la mezcla se concentró y el residuo se mezcló con agua y se extrajo cuatro veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó usando un cartucho de 40 g de gel de sílice (gradiente de 0-10% de diclorometano-metanol en 50 min). Las fracciones limpias del producto se combinaron y se secaron. Se obtuvieron 1,04 g del compuesto del título.

Tr de LC-MS: 2,82 min [M+H$^+$]: 262,1 (met. e)

W1.116

6-(1-Etilpropoxi)-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]ftalazin-3-ilamina

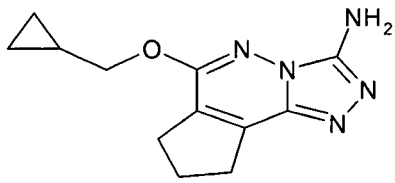


Se cargó inicialmente 3-pentanol (20 ml) en una atmósfera de argón, se mezcló con hidruro sódico (946 mg) y se agitó a 50°Cdurante 1 h. Posteriormente, se añadió lentamente gota a gota hidrobromuro de 6-cloro-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]-ftalazin-3-ilamina (W2.018, 1,88 g), disuelto en 3-pentanol (20 ml) y DMF (100 ml), durante 1 h. Después de agitar durante 1 h, la mezcla se concentró y el residuo se mezcló con agua y se extrajo cuatro veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó usando un cartucho de 40 g de gel de sílice (gradiente de 0-10% de diclorometano-metanol en 50 min). Las fracciones limpias del producto se combinaron y se secaron. Se obtuvieron 0,8 g del compuesto del título.

Tr de LC-MS: 1,15 min [M+H$^+$]: 276,1 (met. a)

W1.120

6-Ciclopropilmetoxi-8,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-3-ilamina

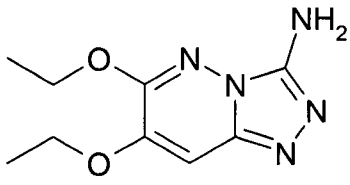


Se cargó inicialmente ciclopropilmetanol (1,78 ml) en DMF (25 ml), Subsiguientemente, la mezcla se combinó con hidruro sódico (541 mg) en una atmósfera de argón y se agitó a 45°C durante 0,5 h. Posteriormente, se disolvió hidrobromuro de 6-cloro-8,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.017, 1,31 g) en DMF (20 ml) y se añadieron en porciones 11,25 ml de la solución de alcóxido a 45°C durante 90 min. Después, la mezcla se agitó a 45°Cdurante otra hora. Después de añadir un poco de agua, la mezcla se secó y se purificó usando gel de sílice (cartucho de 80 g, gradiente de 0-20% de diclorometano/metanol en 60 min). Se obtuvieron 528 mg del compuesto del título.

Tr de LC-MS: 0,63 min [M+H$^+$]: 246,1 (met. b)

W1.125

6,7-Dietoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



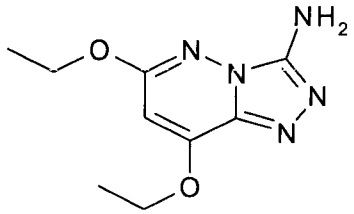
Se cargó inicialmente (5,6-dietoxi-piridazin-3-il)hidrazina (W3.120; 50 mg) en una mezcla de etanol (3,5 ml) y agua (0,75 ml) a TA mientras se agitaba. Después, se añadió cuidadosamente gota a gota bromuro de cianógeno (55 mg, disuelto en 0,75 ml de etanol y 0,15 ml de agua). Después de agitar durante 7 h, la mezcla se dejó en reposo durante una noche. Después, se añadieron 2 equivalentes más de bromuro de cianógeno, disuelto en 0,75 ml de etanol y 0,15 ml de agua, y la mezcla se agitó adicionalmente a TA durante 4 h y después a 55°C durante 8 h. Después de un periodo de refrigeración, el disolvente se retiró y el residuo se mezcló con agua. Después de hacerse alcalino con una solución saturada de carbonato

potásico, se extrajo cuatro veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. El residuo se purificó por medio de HPLC preparativa (met. A). Las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida, se hicieron alcalinas con una solución saturada de carbonato potásico y se extrajeron cuatro veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 36 mg del compuesto del título.

Tr de LC-MS: 0,54 min [M+H$^+$]: 224,2 (met. b)

W1.126

6,8-Dietoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

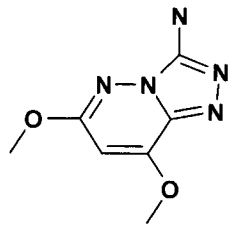


Se disolvió 6-cloro-8-metanosulfonil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W1.132; 60 mg, 0,24 mmol) en etanol (5 ml), se añadió etóxido sódico (500 µl, al 21% en etanol) y la mezcla se calentó a 50°C durante 5 h. La mezcla se concentró y el residuo se purificó por cromatografía ultrarrápida (diclorometano:metanol). Rendimiento: 54 mg

Tr de LC-MS: 0,52 min [M+H$^+$]: 224,1 (met. b)

W1.127

6,8-Dimetoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



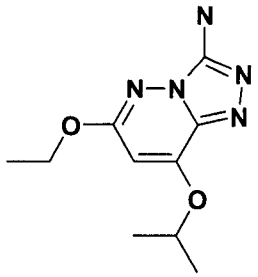
Se disolvió 6-cloro-8-metanosulfonil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.126; 100 mg, 0,40 mmol) en metanol (10 ml), y se añadió una solución de metóxido sódico (0,75 ml, 4,04 mmol). La mezcla se calentó a reflujo durante 3 h, luego se concentró y el residuo se disolvió en agua y se estableció un pH de 6

añadiendo ácido clorhídrico acuoso. La mezcla se extrajo con EA y las fases orgánicas combinadas se secaron y concentraron. El residuo se purificó mediante cromatografía ultrarrápida (diclorometano:metanol). Rendimiento: 30 mg

Tr de LC-MS: 0,14 min [M+H$^+$]: 196,1 (met. b)

W1.128

6-Etoxi-8-isopropoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

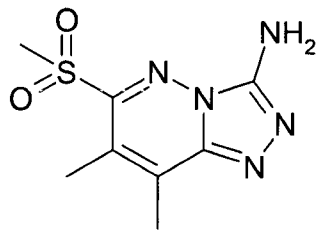


Se disolvió 6,8-dietoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W1.126; 80 mg, 0,358 mmol) en isopropanol (10 ml), y se añadió isopropóxido de sodio (297 mg). La mezcla se calentó hasta 85°C durante 1 h y se concentró, el residuo se disolvió en agua y se estableció un pH de 6 añadiendo ácido clorhídrico acuoso. La mezcla se extrajo con acetato de etilo y las fases orgánicas combinadas se secaron y concentraron. El residuo remanente se purificó mediante cromatografía ultrarrápida (diclorometano:MeOH). Rendimiento: 58 mg

Tr de LC-MS: 0,58 min [M+H$^+$]: 238,2 (met. b)

W1.130

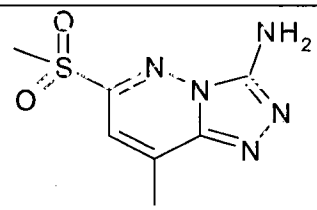
6-Metanosulfonil-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se disolvieron hidrobromuro de 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.006; 1,0 g) y sulfinato sódico (916 mg) en DMF (6 ml) y la mezcla se agitó en un microondas a 150°Cdurante 45 min. Después de que se retirara el disolvente, el residuo se purificó usando gel de sílice (cartucho de 40 g, gradiente de 0-20% de diclorometano/metanol en 60 min). Se obtuvieron 1,02 g del compuesto del título.

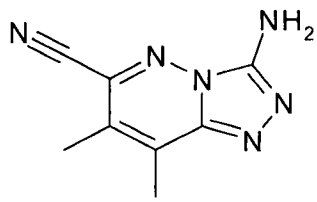
Tr de LC-MS: 0,33 min [M+H$^+$]: 242,1 (met. b)

El siguiente se preparó de manera análoga:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W1.131		0,20 min	175,1 (met. b)	W2.002; 5,1 g, sulfinato (4,9 g); 7 h a 100°C; producto: 6,3 g

W1.135

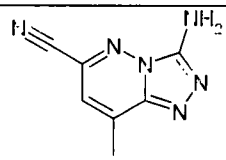
3-Amino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazina-6-carbonitrilo



Se disolvió 6-metanosulfonil-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W1.130; 1,0 g) en DMF (30 ml) y se mezcló con cianuro potásico (405 mg). Después de agitar a 100°C durante 1 h, la mezcla se secó. El residuo se agitó en EA y se cromatografió usando una columna corta de gel de sílice con EA. Las fracciones se concentraron por evaporación rotatoria. Se obtuvieron 560 mg del compuesto del título.

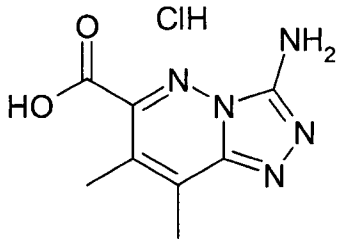
Tr de LC-MS: 0,27 min [M+H$^+$]: 189,1 (met. b)

El siguiente se preparó de manera análoga:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W1.136		0,20 min	175,1 (met. b)	W1.131 6,3 g, KCN (2,7 g); 7 h a 100°C; producto: 870 mg

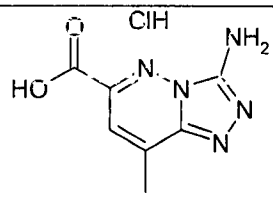
W1.140

Hidrocloruro del ácido 3-amino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazina-6-carboxílico



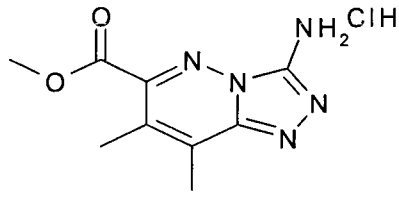
Se mezcló 3-amino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazina-6-carbonitrilo (W1.135; 600 mg) con ácido clorhídrico concentrado (20 ml) y se mantuvo a la temperatura de reflujo durante 5 h. Posteriormente, el ácido clorhídrico se retiró y el residuo se recogió con agua y se liofilizó. Se obtuvieron 790 mg del compuesto del título, que tenía suficiente pureza para la siguiente reacción. Tr de LC-MS: 0,19 min [M+H$^+$]: 189,1 (met. c)

El siguiente se preparó de manera análoga:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W1.41		0,11 min	194,1 (met. b)	W1.136 860 mg; HCl (30 ml); 2 h RF; producto: 1,7 g

W1.145

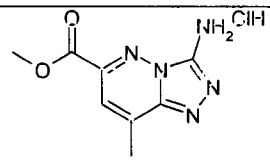
Hidrocloruro de 3-amino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazina-6-carboxilato de metilo



Se disolvió hidrocloruro del ácido 3-amino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazina-6-carboxílico (W1.140; 780 mg) en metanol (40 ml), se añadió lentamente gota a gota cloruro de tionilo (1,9 ml) y después la mezcla se agitó a 65°C. Después de 2,5 h, la mezcla se secó y el residuo se purificó usando gel de sílice (cartucho de 24 g, gradiente de 0-20% de diclorometano/metanol en 60 min). Se obtuvieron 602 mg del compuesto del título.

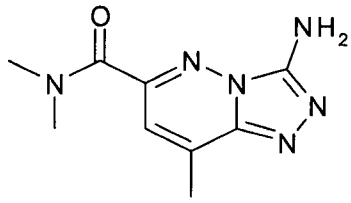
Tr de LC-MS: 0,37 min [M+H$^+$]: 222,1 (met. b)

El siguiente se preparó de manera análoga:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W1.146		0,20 min	208,1 (met. b)	W1.141 600 mg; cloruro de tionilo (1,53 ml); 1,5 h 65°C; producto: 429 mg

W1.150

N-Metil-3-amino-8-metil-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida

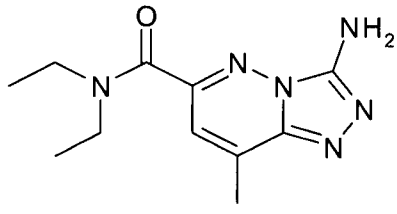


Se disolvió 3-amino-8-metil-[1,2,4]triazolo[4,3-b]piridazina-6-carboxilato de metilo (W1.146; 210 mg) en metanol (4 ml), se enfrió a 0°C, se mezcló lentamente gota a gota con dimetilamina (2,02 ml; 2 M en THF) y se agitó a 0°C. Después de 3 h, se añadieron 5 equivalentes más de una solución de dimetilamina y la mezcla se agitó a 40°C durante 4 h. Después de dejar en reposo durante una noche, se añadieron 5 equivalentes más de una solución de dimetilamina y la mezcla se agitó a 40°C durante 8 h más. Después de dejar en reposo de nuevo durante una noche, se añadieron 5 equivalentes más de una solución de dimetilamina y después la mezcla se agitó a 100°C en un microondas durante 30 min. Posteriormente, la mezcla se concentró y se purificó usando gel de sílice (cartucho de 24 g, gradiente de 0-20% de diclorometano/metanol en 60 min). Se obtuvieron 92 mg del compuesto del título.

Tr de LC-MS: 0,13 min [M+H$^+$]: 221,1 (met. b)

W1.152

N-Etil-3-amino-8-metil-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida

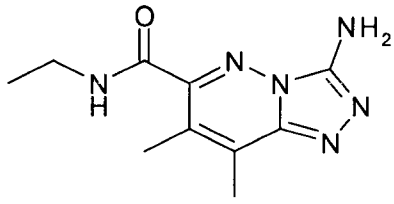


Se disolvió hidrocloruro del ácido 3-amino-8-metil-[1,2,4]triazolo[4,3-b]piridazina-6-carboxílico (W1.141; 300 mg) en DMF (6 ml) y se mezcló con tetrafluoroborato de

O-[(etoxicarbonil)-cianometilenoamino]-N,N,N',N'-tetrametiluronio (TOTU; 429 mg) y dietilamina (573 mg). Después de 2 h, la DMF se retiró y el residuo se purificó usando gel de sílice (cartucho de 24 g, gradiente de 0-20% de diclorometano/metanol en 60 min). El producto se recogió con agua y se liofilizó. Con el fin de retirar la dietilamina residual, la mezcla se cromatografió usando una columna corta (95:5 de diclorometano/metanol). Se obtuvieron 112 mg del compuesto del título, que aún estaba contaminado con dietilamina. Tr de LC-MS: 0,40 min [M+H$^+$]: 249,1 (met. b)

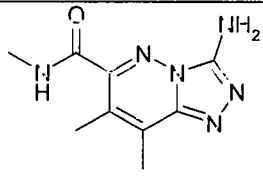
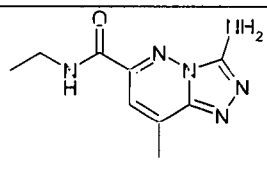
W1.154

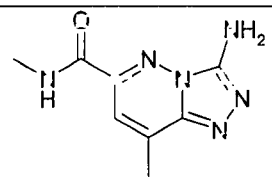
N-Etil-3-amino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida



Se disolvió hidrocloruro de 3-amino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazina-6-carboxilato de metilo (W1.145; 200 mg) en metanol, se enfrió a 0°C, se mezcló lentamente gota a gota con etilamina (1,81 ml; 2 M en THF) y se agitó a 0°C durante 6 h. Después, se añadió un equivalente adicional de etilamina y la mezcla se dejó en reposo a TA durante el fin de semana. Posteriormente, la mezcla se concentró y se purificó usando gel de sílice (cartucho de 24 g, gradiente de 0-20% de diclorometano/metanol en 60 min). Se obtuvieron 149 mg del compuesto del título. Tr de LC-MS: 0,21 min [M+H$^+$]: 235,1 (met. b)

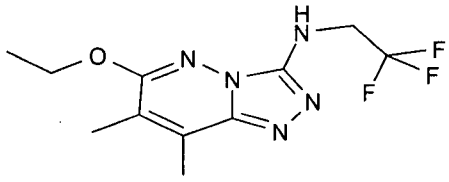
Los siguientes se prepararon de manera análoga:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W1.155		0,58 min	221,1 (met. c)	W1.145 200 mg; metilamina (2 M en THF); producto: 113 mg
W1.156		0,28 min	221,1 (met. b)	W1.146 210 mg; etilamina (4,7 equiv.; 2 M en THF); producto: 164 mg

W1.157		0,16 min	207,1 (met. b)	W1.146 225 mg; metilamina (4,7 equiv.; 2 M en THF); producto: 113 mg

W1.165

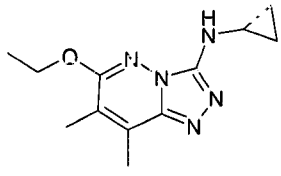
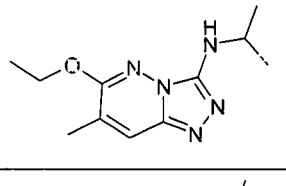
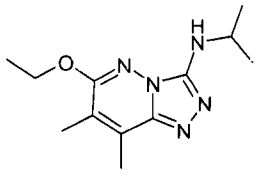
(6-Etoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-il)(2,2,2-trifluoroetil)amina

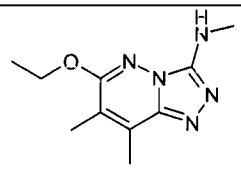
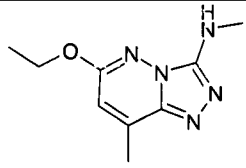


Se cargó inicialmente (6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-il)(2,2,2-trifluoroetil)amina (W2. ; 330 mg) en etanol (25 ml) y se mezcló con etóxido sódico (90 mg). La mezcla de reacción se agitó a 50°C durante 4 h, después se añadió adicionalmente etóxido sódico (10 mg) y la mezcla se agitó adicionalmente a 50°Cdurante 3 h. Después de dejar en reposo durante una noche, la mezcla se mezcló con agua y se secó. El residuo se recogió en EA y se lavó tres veces con agua. La fase de EA se secó sobre sulfato sódico, se filtró y se concentró. Se obtuvieron 340 mg del compuesto del título.

Tr de LC-MS: 0,82 min [M+H$^+$]: 290,2 (met. b)

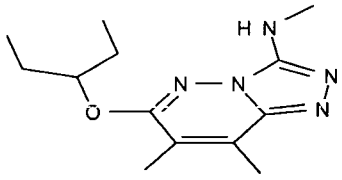
Los siguientes se prepararon de manera análoga:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W1.166		0,75 min	248,2 (met. b)	W2.166; 690 mg; producto: 508 mg
W1.167		0,73 min	236,2 (met. b)	W2.167; 500 mg; producto: 380 mg
W1.168		0,78 min	250,2 (met. b)	W2.168; 78 mg; producto: 57 mg

W1.169		0,71 min	222,2 (met. b)	W2.169; 50 mg; producto: 27 mg
W1.170		0,49 min	208,2 (met. b)	W2.170; 105 mg; producto: 70 mg

W1.175

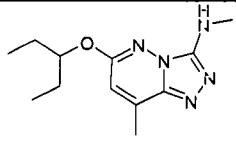
[6-(1-Etilpropoxi)-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-il]metilamina



Se cargó inicialmente 3-pentanol (1,2 ml) a TA con agitación. Después, se añadió hidruro sódico (77 mg) mientras se enfriaba con hielo. Después de agitar a 55°Cdurante 3 h, se añadió gota a gota (6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-il)metilamina (W2.169; 50 mg), disuelta en 3-pentanol (1 ml) y DMF abs. (2 ml). Después de agitar durante 2 h, la mezcla de reacción se dejó en reposo a TA durante una noche, se mezcló con agua y diclorometano y después se extrajo tres veces más con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 44 mg del compuesto del título.

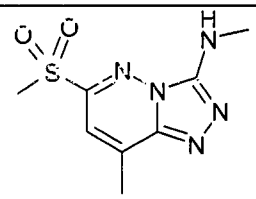
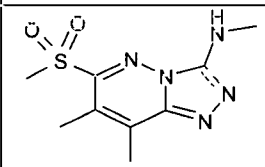
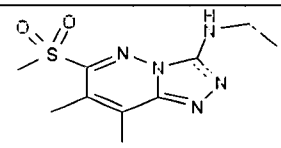
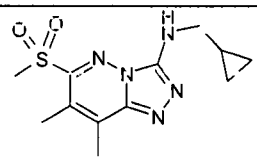
Tr de LC-MS: 0,86 min [M+H$^+$]: 264,2 (met. b)

El siguiente se preparó de manera análoga:

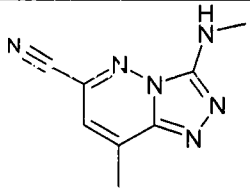
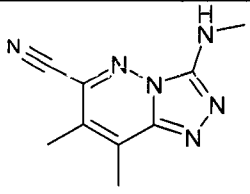
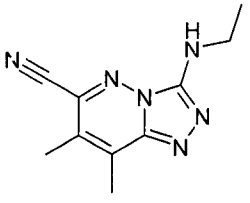
Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W1.176		0,82 min	250,2 (met. b)	W2.170; 105 mg; producto: 60 mg

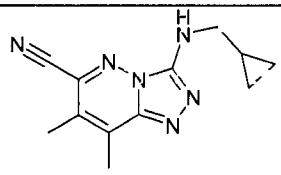
Los siguientes se prepararon de forma análoga a W1.130:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:

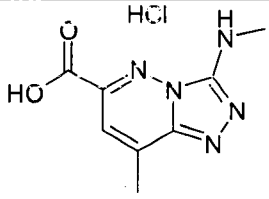
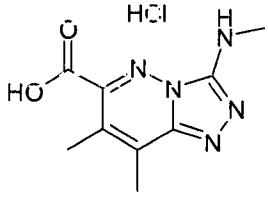
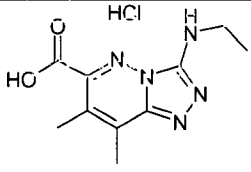
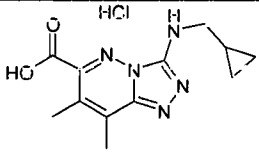
W1.189		0,24 min	242,1 (met. b)	W2.170; 7,73 g, producto: 6,22 g
W1.190		0,43 min	256,0 (met. b)	W2.169 7,08 g; producto: 4,84 g
W1.191		0,51 min	270,1 (met. b)	W2.191 7,89 g; producto: 5,38 g
W1.192		0,60 min	296,1 (met. b)	W2.191 9,44 g; producto: 5,45 g

Los siguientes se prepararon de forma análoga a W1.135:

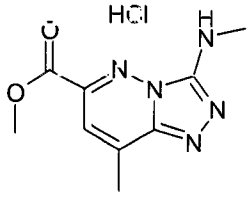
Número		Tr de LC-MS	$[M+H^+]$:	Comentario:
W1.199		0,24 min	189,1 (met. b)	W1.189 5,00 g, producto: 1,74 g
W1.200		0,39 min	203,1 (met. b)	W1.190 4,83 g; producto: 3,50 g
W1.201		0,50 min	217,1 (met. b)	W1.191 5,37 g; producto: 3,18 g

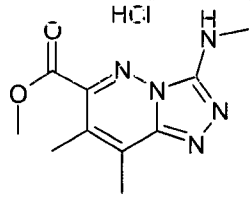
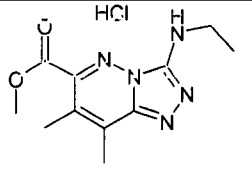
W1.202		0,68 min	243,1 (met. b)	W1.192 5,44 g; producto: 3,84 g

Los siguientes se prepararon de forma análoga a W1.140:

Número		Tr de LC-MS	$[M+H^+]$:	Comentario:
W1.209		0,10 min	208,1 (met. b)	W1.199: 1,73 g, producto: 2,77 g
W1.210		0,23 min	222,1 (met. c)	W1.200 3,50 g; producto: 5,27 g
W1.211		0,47 min	236,1 (met. c)	W1.201 3,17 g; producto: 4,68 g
W1.212		0,17 min	262,1 (met. b)	W1.202 3,83 g; producto: 5,47 g

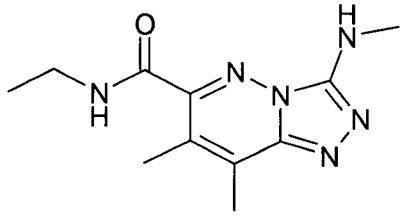
Los siguientes se prepararon de forma análoga a W1.145:

Número		Tr de LC-MS	$[M+H^+]$:	Comentario:
W1.219		0,29 min	222,1 (met. b)	W1.210 2,77 g; producto: 2,56 g

W1.220		0,41 min	236,1 (met. b)	W1.210 4,98 g; producto: 4,11 g
W1.221		0,50 min	250,1 (met. b)	W1.211 4,67 g; producto: 4,06 g

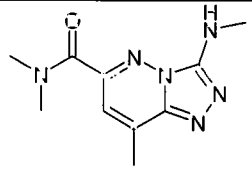
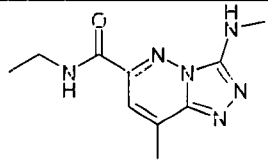
W1.250

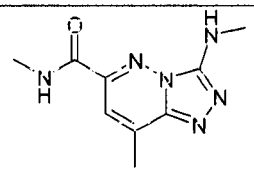
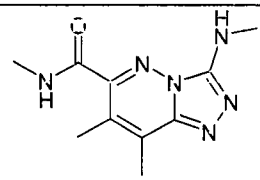
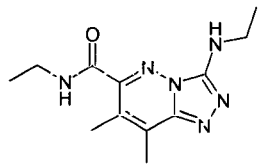
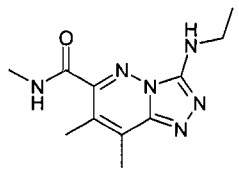
N-Etil-7,8-dimetil-3-metilamino-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida



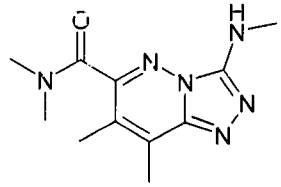
Se disolvió hidrocloruro de 7,8-dimetil-3-metilamino-[1,2,4]triazolo[4,3-b]piridazina-6-carboxilato de metilo (W1.220; 1,3 g) en metanol (30 ml), se enfrió a 0°C, se mezcló lentamente gota a gota con etilamina (11,44 ml; 2 M en THF) y se agitó a 0°C durante 6 h. Después, se añadieron cuatro equivalentes más de etilamina y la mezcla se dejó en reposo a TA durante el fin de semana. Posteriormente, la mezcla se concentró y se purificó usando gel de sílice (cartucho de 40 g, gradiente de diclorometano/metanol de 0-20% en 60 min). Se obtuvieron 1,12 g del compuesto del título. Tr de LC-MS: 0,81 min [M+H$^+$]: 249,1 (met. b)

Los siguientes se prepararon de manera análoga:

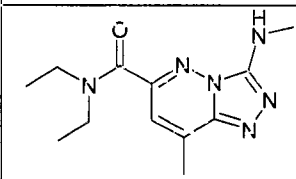
Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W1.251		0,14 min	235,1 (met. b)	W1.219; 770 mg; dimetilamina (5+2 equiv.; 2 M en THF); producto: 542 mg
W1.252		0,39 min	235,1 (met. b)	W1.219; 850 mg; etilamina (4,7 equiv.; 2 M en THF); producto: 590 mg

W1.253		0,18 min	221,1 (met. b)	W1.219; 850 mg; metilamina (4,7+2 equiv.; 2 M en THF); producto: 530 mg
W1.254		0,68 min	235,1 (met. b)	W1.220; 800 mg; metilamina (4,7+2 equiv.; 2 M en THF); producto: 629 mg
W1.255		0,86 min	263,1 (met. b)	W1.221; 800 mg; etilamina (4,7+4 equiv.; 2 M en THF); producto: 732 mg
W1.256		0,79 min	249,1 (met. b)	W1.221; 800 mg; metilamina (4,7+2 equiv.; 2 M en THF); producto: 612 mg

W1.265 se preparó de forma análoga a W1.150:

Número		Tr de LC-MS	$[M+H^+]$:	Comentario:
W1.265		0,16 min	249,1 (met. b)	W1.220; 800 mg; dimetilamina (5+5+5 equiv., 2 M en THF); producto: 330 mg

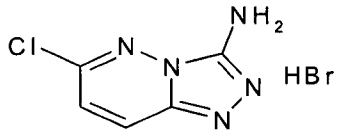
El siguiente se preparó de forma análoga a W1.152:

Número		Tr de LC-MS	$[M+H^+]$:	Comentario:
W1.270		0,45 min	263,1 (met. b)	W1.209; 860 mg; dietilamina (1,81 ml); TOTU 1,16 g; producto: 251 mg (sin liofilización ni columna adicional)

W2.

W2.001

Hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



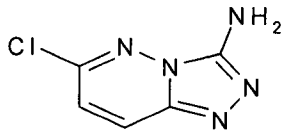
Se disolvió 3-(cloroiridazin-6-il)hidrazina (5 g) en una mezcla de EtOH (90 ml) y agua (36 ml) a TA mientras se agitaba. Después, se añadió cuidadosamente gota a gota una solución 5 M de bromuro de cianógeno (13 ml en acetonitrilo). Después de agitar durante 4,5 h, la mezcla se dejó en reposo durante una noche y, al día siguiente, se añadió más cantidad de una solución 5 M de bromuro de cianógeno (3 ml en acetonitrilo) mientras se agitaba. Después de 4 h más de agitación, el precipitado formado se retiró por filtración con succión y se secó. Se obtuvieron 6,1 g del compuesto del título.

Las aguas madre se mezclaron con MtB éter y el precipitado formado se retiró por filtración con succión y se secó, para obtener 1,5 g más del compuesto del título.

Tr de LC-MS: 0,23 min [M+H$^+$]: 170,0 (met. a)

W2.001a

6-Cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

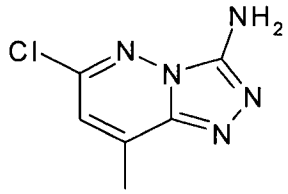


Se recogió hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001; 1,1 g) con una gran cantidad de agua y se hizo alcalino con una solución saturada de carbonato potásico. El sólido que precipitó se retiró por filtración con succión y se secó (308 mg). La extracción repetida de las aguas madre con diclorometano, el secado de las fases orgánicas combinadas sobre sulfato sódico, la filtración y la concentración produjeron 228 mg más de producto en total.

Tr de LC-MS: 0,23 min [M+H$^+$]: 170,1 (met. a)

W2.002

Hidrobromuro de 6-cloro-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



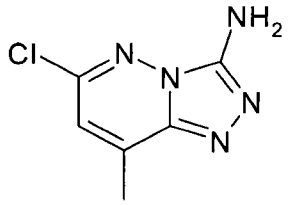
HBr

Se cargó inicialmente (6-cloro-4-metilpiridazin-3-il)hidrazina (W3.002; 4,6 g) en EtOH (330 ml) y agua (70 ml) mientras se agitaba a TA. Después, se añadió lentamente gota a gota bromuro de cianógeno en una mezcla de EtOH (170 ml) y agua (30 ml) a TA. Después de agitar a TA durante 6 h, la mezcla se dejó en reposo durante una noche. Después, la mezcla se secó y el residuo se purificó usando gel de sílice (cartucho de 40 g, gradiente de 0-10% de DCM/metanol en 30 min). Se obtuvieron 7,3 g del compuesto del título.

Tr de LC-MS: 0,51 min [M+H$^+$]: 184,1 (met. a)

W2.002b

Sal del ácido trifluoroacético de 6-cloro-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



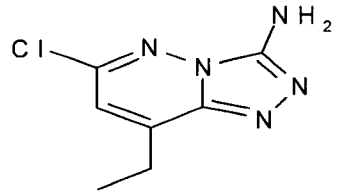
TFA

Se cargó inicialmente (6-cloro-4-metilpiridazin-3-il)hidrazina (W3.002; 432 mg) en una mezcla de etanol (15 ml) y agua (3 ml) mientras se agitaba a TA. Después, se añadió cuidadosamente gota a gota bromuro de cianógeno (531 mg, disuelto en 7 ml de EtOH y 1,5 ml de agua). Después de agitar durante 2 h, la mezcla se dejó en reposo durante una noche. Después, la mezcla se agitó a TA durante 4 h más y después a 50°C durante 2 h. Después de enfriar durante una noche, el disolvente se retiró y el residuo se purificó por medio de HPLC preparativa (met. A). Las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida y se liofilizaron. Se obtuvieron 158 mg del compuesto del título.

Tr de LC-MS: 0,44 min [M+H$^+$]: 184,1 (met. a)

W2.003

6-Cloro-8-etil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

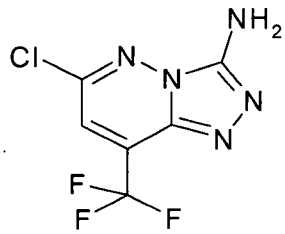


Se cargó inicialmente trifluoroacetato de (6-cloro-4-etilpiridazin-3-il)hidrazina (W3.003; 1,35 g) en EtOH (25 ml) y agua (4 ml) mientras se agitaba a TA. Después, se añadió cuidadosamente gota a gota bromuro de cianógeno (997 mg), disuelto en EtOH (5 ml)-agua (2 ml). Después de agitar a temperatura ambiente durante 8 h y de un periodo de reposo de una noche, la mezcla se agitó a 55°C durante 4 h más. Posteriormente, el disolvente se concentró y el residuo se mezcló con agua. Una vez que se hizo alcalina con una solución saturada de carbonato potásico, la mezcla se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 918 mg del compuesto del título.

Tr de LC-MS: 0,35 min [M+H$^+$]: 198,1 (met. b)

W2.004

6-Cloro-8-trifluorometil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

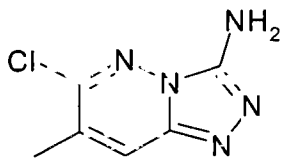
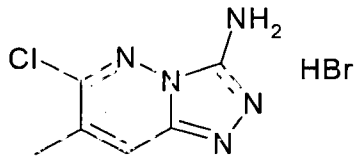


Hidrocloruro de (6-cloro-4-trifluorometilpiridazin-3-il)-hidrazina (W3.004; 85 mg) se convirtió y se sometió a tratamiento de forma análoga a W2.003. Sin embargo, la mezcla se agitó durante 8 h a TA y luego se dejó en reposo durante el fin de semana para completar la reacción.

Tr de LCMS: 0,41 min [M+H$^+$]: 238,1 (met. b)

W2.005 y W2.005a

6-Cloro-7-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina e hidrobromuro de 6-cloro-7-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

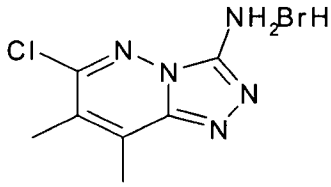



(6-Cloro-5-metilpiridazin-3-il)-hidrazina (W3.005; 4,68 g) se convirtió y se sometió a tratamiento de forma análoga a W2.002. La purificación se efectuó utilizando gel de sílice (cartucho de 80 g, gradiente de DCM/metanol de 0-10% en 60 min). Se aislaron 1,88 g de la base libre. El aclarado del gel de sílice proporcionó de nuevo 2,67 g del hidrobromuro.

Tr de LCMS: 0,46 min [M+H$^+$]: 184,1 (met. a)

W2.006

Hidrobromuro de 6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

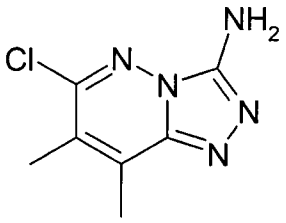


Se cargó inicialmente (6-cloro-4,5-dimetilpiridazin-3-il)hidrazina (W3.006; 12 g) en EtOH (240 ml) y agua (50 ml) mientras se agitaba a TA. Después, se añadió lentamente gota a gota a TA bromuro de cianógeno (14,7 g) en una mezcla de EtOH (120 ml) y agua (25 ml). Después de agitar a TA durante 6 h, la mezcla se dejó en reposo durante una noche. Después, la mezcla se secó y el residuo se purificó usando gel de sílice (cartucho de 80 g, gradiente de 0-20% de DCM/metanol en 60 min). Se obtuvieron 19,4 g del compuesto del título.

Tr de LC-MS: 0,28 min [M+H$^+$]: 196,1 (met. b)

W2.006a

6-Cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



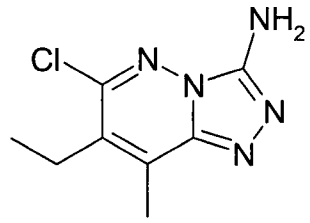
(6-Cloro-4,5-dimetilpiridazin-3-il)-hidrazina (W3.006; 519 mg) se convirtió y se sometió a tratamiento de forma análoga a W2.007. Se aislaron 570 mg de la base

libre.

Tr de LCMS: 1,35 min [M+H$^+$]: 198,0 (met. e)

W2.007

6-Cloro-7-etil-8-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

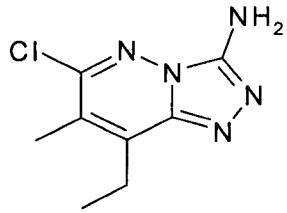


Se disolvió (6-cloro-5-etil-4-metil-piridazin-3-il)-hidrazina (W8.007; 340 mg) en etanol/agua (10/2 ml) a TA mientras se agitaba. Después, se añadió cuidadosamente gota a gota bromuro de cianógeno (386 mg, disuelto en 5 ml de etanol y 1 ml de agua). Después de agitar a TA durante 5 h, la mezcla se dejó en reposo durante una noche y después el disolvente se retiró y el residuo se mezcló con agua. Una vez que se hizo alcalino el residuo con una solución saturada de carbonato potásico, se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de retirar por filtración el desecante, se secaron a presión reducida. Se obtuvieron 385 mg del compuesto del título.

Tr de LCMS: 0,62 min [M+H$^+$]: 212,1 (met. b)

W2.008

6-Cloro-8-etil-7-metil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



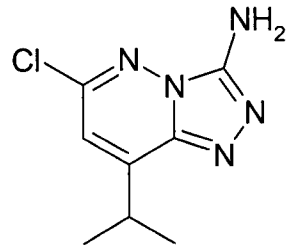
Se cargó inicialmente sal del ácido trifluoroacético de (6-cloro-4-etil-5-metilpiridazin-3-il)hidrazina (W8.008; 340 mg) en una mezcla de EtOH (12 ml) y agua (2 ml) a TA mientras se agitaba. Después, se añadió cuidadosamente gota a gota bromuro de cianógeno (240 mg), disuelto en 3 ml de EtOH y 1 ml de agua, y la mezcla se agitó durante 8 h. Después de dejar en reposo durante una noche, se añadieron 0,5 equiv. de una solución de bromuro de cianógeno y la mezcla se agitó de nuevo a TA durante 4,5 h y después a 55°C durante 2 h. Después de dejar en reposo

durante una noche, el disolvente se retiró y el residuo se mezcló con agua. Una vez que se hizo alcalina con una solución saturada de carbonato potásico, la mezcla se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 270 mg del compuesto del título.

Tr de LC-MS: 0,54 min [M+H$^+$]: 212,1 (met. b)

W2.009

6-Cloro-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



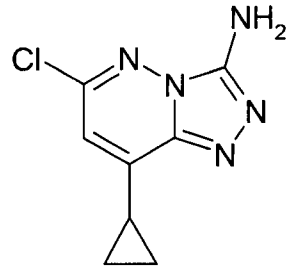
Se cargó inicialmente sal del ácido trifluoroacético de (6-cloro-4-isopropil-piridazin-3-il)-hidrazina (W3.009; 258 mg) en etanol/agua (6/1 ml) a TA mientras se agitaba. Después, se añadió cuidadosamente gota a gota bromuro de cianógeno (182 mg, disuelto en 1,5 ml de etanol y 0,5 ml de agua). Después de agitar durante 5 horas, la mezcla se dejó en reposo durante una noche, se añadió 1 equiv. de la solución de bromuro de cianógeno y la mezcla se agitó todo el día. Después de dejar en reposo durante una noche, el disolvente se retiró y el residuo se mezcló con agua. Una vez que se hizo alcalino el residuo con una solución saturada de carbonato potásico, se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 180 mg del compuesto del título con suficiente pureza.

Tr de LCMS: 0,65 min [M+H$^+$]: 212,1 (met. b)

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 6,98 (1 H), 6,63 (2 H), 3,37 (1 H), 1,35 (6 H)

W2.010

6-Cloro-8-ciclopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

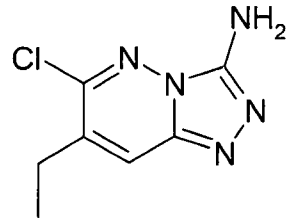


Sal del ácido trifluoroacético de (6-cloro-4-ciclopropil-piridazin-3-il)-hidrazina (W3.010; 400 mg) se convirtió y se sometió a tratamiento de forma análoga a W2.009. Sin embargo, se añadió otro equivalente adicional de bromuro de cianógeno y la mezcla se agitó adicionalmente durante 6 h a 55°C. Se obtuvieron 252 mg del compuesto del título.

Tr de LCMS: 0,51 min [M+H$^+$]: 210,1 (met. b)

W2.011

6-Cloro-7-etil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

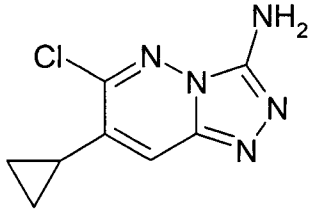


Sal del ácido trifluoroacético de (6-cloro-5-etilpiridazin-3-il)hidrazina (W3.011; 169 mg) se convirtió y se sometió a tratamiento de forma análoga a W2.009. Se obtuvieron 130 mg del compuesto del título con suficiente pureza.

Tr de LCMS: 0,33 min [M+H]$^+$: 198,1 (met. b)

W2.012

6-Cloro-7-ciclopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



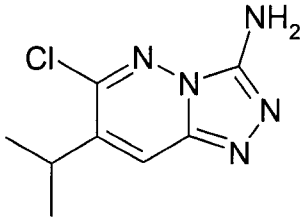
Sal del ácido trifluoroacético de (6-cloro-5-ciclopropilpiridazin-3-il)hidrazina (W3.012; 400 mg) se convirtió y se sometió a tratamiento de forma análoga a W2.008, excepto que, en lugar de 0,5, se añadió un equivalente adicional de solución de bromuro de cianógeno. Se obtuvieron 260 mg del compuesto del título con

suficiente pureza.

Tr de LCMS: 0,45 min [M+H]$^+$: 210,1 (met. b)

W2.013

6-Cloro-7-isopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



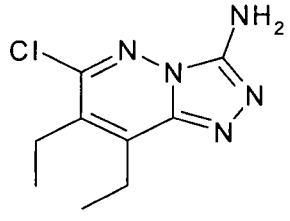
Sal del ácido trifluoroacético de (6-cloro-5-isopropilpiridazin-3-il)hidrazina (W3.013; 400 mg) se cargó inicialmente en etanol/agua (6/1 ml) a TA al tiempo que se agitaba. Después, se añadió cuidadosamente, gota a gota, bromuro de cianógeno (353 mg, disuelto en una mezcla de 1 ml de EtOH y 0,5 ml de agua). Después de agitar durante 5 horas, la mezcla se dejó en reposo durante una noche y se agitó durante otro día. Después de reposar durante una noche, el disolvente se retiró y el residuo se mezcló con agua. Una vez que se hizo alcalino el residuo con una solución saturada de carbonato potásico, se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 400 mg del compuesto del título con suficiente pureza.

Tr de LCMS: 0,65 min [M+H]$^+$: 212,1 (met. b)

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,97 (1 H), 6,61 (2 H), 3,11 (1 H), 1,25 (6 H)

W2.014

6-Cloro-7,8-dietil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

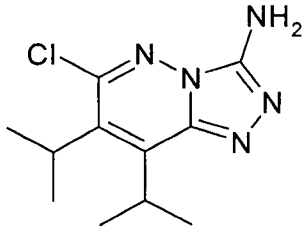


(6-Cloro-4,5-dietilpiridazin-3-il)hidrazina (W3.014; 2,0 g) se convirtió y se sometió a tratamiento de forma análoga a W2.007. Se obtuvieron 2,20 g del compuesto del título con suficiente pureza.

Tr de LCMS: 0,72 min [M+H]$^+$: 226,1 (met. b)

W2.015

6-Cloro-7,8-diisopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

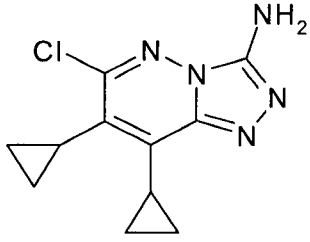


(6-Cloro-4,5-diisopropilpiridazin-3-il)hidrazina (W3.015; 274 mg) se convirtió y se sometió a tratamiento de forma análoga a W2.007. Se obtuvieron 290 mg del compuesto del título con suficiente pureza.

Tr de LCMS: 0,87 min [M+H]$^+$: 254,2 (met. b)

W2.016

6-Cloro-7,8-diciclopropil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

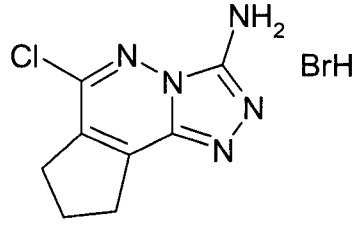


(6-Cloro-4,5-diciclopropilpiridazin-3-il)hidrazina (W3.016; 346 mg) se convirtió y se sometió a tratamiento de forma análoga a W2.007. Se obtuvieron 335 mg del compuesto del título con suficiente pureza.

Tr de LCMS: 0,81 min [M+H]$^+$: 250,1 (met. b)

W2.017

Hidrobromuro de 6-cloro-8,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-3-ilamina

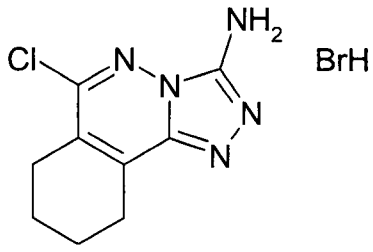


(4-Cloro-6,7-dihidro-5H-ciclopenta[d]piridazin-1-il)hidrazina (W3.017; 3,85 g) se convirtió y se sometió a tratamiento de forma análoga a W2.006. Se obtuvieron 5,44 g del compuesto del título con suficiente pureza.

Tr de LCMS: 0,74 min [M+H]$^+$: 210,1 (met. a)

W2.018

Hidrobromuro de 6-cloro-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]ftalazin-3-ilamina

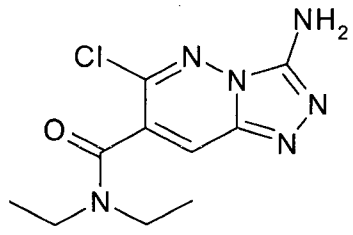


(4-Cloro-5,6,7,8-tetrahidroftalazin-1-il)hidrazina (W3.018; 4,00 g) se convirtió y se sometió a tratamiento de forma análoga a W2.006. Se obtuvieron 5,16 g del compuesto del título

Tr de LCMS: 0,82 min [M+H]$^+$: 224,1 (met. a)

W2.019

N,N-Dietil-3-amino-6-cloro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida

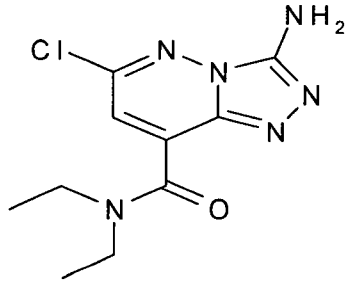


Sal del ácido N,N-dietil-3-cloro-6-hidrazinopiridazina-4-carboxamida-trifluoroacético (W3.019; 390 mg) se convirtió y se sometió a tratamiento de forma análoga a W2.007. Se obtuvieron 285 mg del compuesto del título con suficiente pureza.

Tr de LCMS: 0,94 min [M+H]$^+$: 269,1 (met. a)

W2.020

N,N-Dietil-3-amino-6-cloro-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida



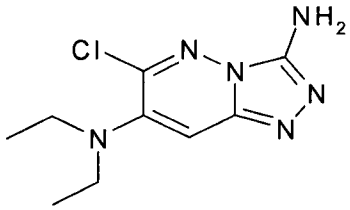
Sal del ácido N,N-dietil-6-cloro-3-hidrazinopiridazina-4-carboxamida (W3.020; 320

mg) se convirtió y se sometió a tratamiento de forma análoga a W2.007. Se obtuvieron 222 mg del compuesto del título con suficiente pureza.

Tr de LCMS: 0,93 min [M+H]$^+$: 269,1 (met. a)

W2.021

6-Cloro-N*7*,N*7*-dietil-[1,2,4]triazolo[4,3-b]piridazina-3,7-diamina

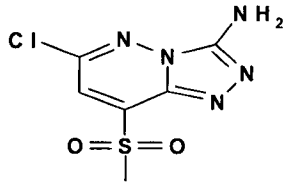


(3-Cloro-6-hidrazinopiridazin-4-il)dietilamina (W3.021; 215 mg) se convirtió de forma análoga a W2.007, y se retiró la mezcla de disolventes. El residuo se purificó mediante HPLC preparativa (met. A). Las fracciones de producto, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo bajo presión reducida, se ajustaron a pH 9 con hidrógeno-carbonato de sodio y se extrajeron cinco veces con DCM. Las fases orgánicas reunidas se secaron sobre sulfato de magnesio y, después de separar por filtración el desecante, se secaron a presión reducida. Se obtuvieron 94 mg del compuesto del título con suficiente pureza.

Tr de LCMS: 1,04 min [M+H]$^+$: 241,1 (met. a)

W2.126

6-Cloro-8-metanosulfonil-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina

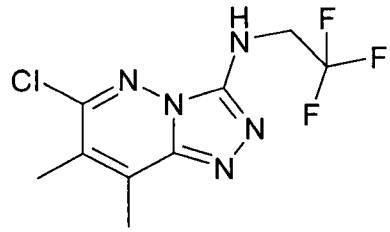


Se disolvió (6-cloro-4-metanosulfonilpiridazin-3-il)hidrazina (W3.126; 200 mg, 0,9 mmol) en metanol (5 ml), se añadió bromuro de cianógeno (360 µl, 3 M en DCM) y la mezcla se agitó a TA durante 4 h. La mezcla se concentró y el residuo se purificó por cromatografía ultrarrápida (diclorometano:metanol). Rendimiento: 111 mg.

Tr de LC-MS: 0,51 min [M+H$^+$]: 227,0 (met. c)

W2.150

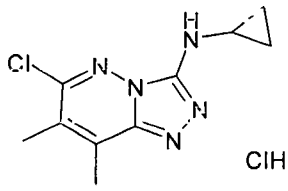
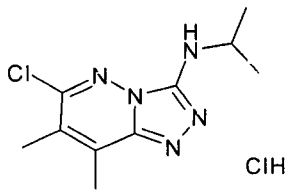
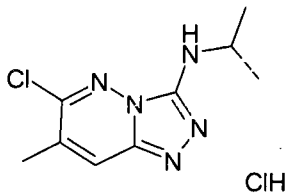
(6-Cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-il)-(2,2,2-trifluoroetil)amina



N'-(6-Cloro-4,5-dimetilpiridazin-3-il)amino-N-(2,2,2-trifluoroetil)urea (W3.150; 400 mg) se disolvió en oxicloruro de fósforo (10 ml) y se calentó hasta 80°C al tiempo que se agitaba. Después de agitar a 80°C durante 7 h, la mezcla se dejó reposar durante una noche y luego se retiró el oxicloruro de fósforo. El residuo se disolvió en agua/DCM y se ajustó hasta pH 9 con hidrógeno-carbonato de sodio, y las fases se separaron. La fase acuosa se extrajo tres veces con DCM, y los extractos combinados se lavaron con solución saturada de cloruro de sodio, se secaron sobre carbonato de sodio, se filtraron y concentraron. Se obtuvieron 330 mg del compuesto del título.

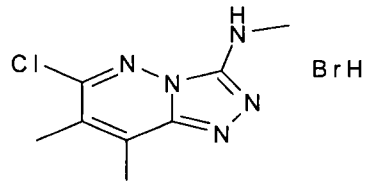
Tr de LC-MS: 0,83 min [M+H]$^+$: 280,1 (met. b)

De forma análoga a W2.169, se prepararon:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W2.166		0,64 min	238,1 (met. b)	W3.166 830 mg; purificación por medio de HPLC(met. D); producto: 690 mg
W2.167		0,71 min	240,2 (met. b)	W3.168 540 mg; purificación por medio de HPLC(met. D); producto: 507 mg
W2.168		0,68 min	226,1 (met. b)	W3.168 140 mg; purificación por medio de HPLC(met. D); producto: 82 mg

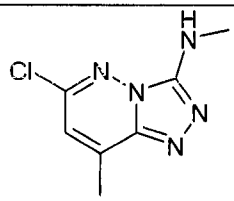
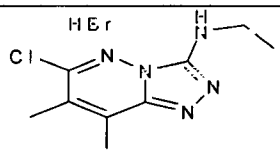
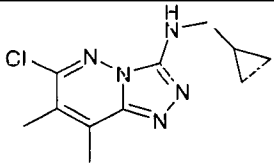
W2.169

Hidrobromuro de (6-cloro-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-3-il)metilamina



Se disolvió N'-(6-cloro-4,5-dimetil-piridazin-3il)-amino-N-metil-tiourea (W3.169; 11,25 g) en etanol (400 ml), se mezcló con bromoacetato de etilo (5,57 ml) y se mantuvo a la temperatura de reflujo con exclusión de la humedad. Después de 2 h, el disolvente se retiró y el residuo se purificó usando gel de sílice (cartucho de 120 g, gradiente de 0-10% de DCM/metanol en 60 min). Se obtuvieron 10,9 g del compuesto del título. Tr de LC-MS: 0,35 min [M+H$^+$]: 212,1 (met. b)

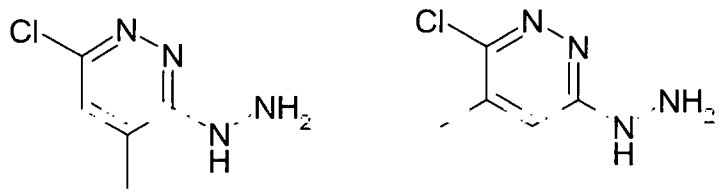
Los siguientes se prepararon de forma análoga a W2.169:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
W2.170		0,24 min	198,1 (met. b)	W3.170 7,74 g; producto: 7,93 g
W2.191		0,50 min	226,1 (met. b)	W3.191 7,61 g; producto: 7,89 g
W1.192		0,60 min	252,1 (met. b)	W3.192 7,80 g; producto: 9,44 g

W3

W3.002

(6-Cloro-4-metilpiridazin-3-il)hidrazina

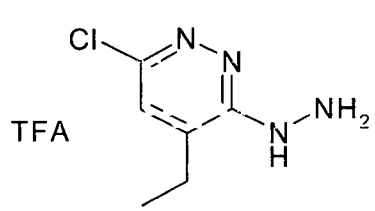


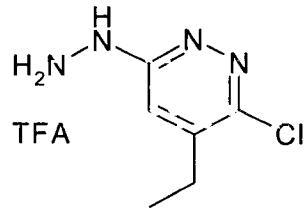
Se sintetizó de forma análoga al documento US 4.578.464

Tr de LC-MS: 0,21 min [M+H$^+$]: 159,1 (met. a)

W3.003 y W3.011

Trifluoroacetato de (6-cloro-4-etilpiridazin-3-il)hidrazina y trifluoroacetato de (6-cloro-5-etilpiridazin-3-il)hidrazina





Se dividió 3,6-dicloro-4-etilpiridazina (W4.003, 2 x 2,4 g) entre 2 recipientes para microondas y cada uno se mezcló con una mezcla de hidrazina monohidrato (6 ml) y dioxano (7 ml). La mezcla de reacción se mantuvo en el microondas a 130°Cdurante 1 h. Posteriormente, el contenido de los dos recipientes se combinó en un matraz de fondo redondo y se secó. El residuo se mezcló con agua y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. El proceso de trabajo se repitió dos veces más. El residuo obtenido de esta manera se separó por medio de HPLC preparativa (método A, con la excepción de que el gradiente fue agua al 100%+TFA al 0,05% → acetonitrilo al 15%/agua al 85%+TFA al 0,05% en 25 min.). Las fracciones del producto, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo a presión reducida y se liofilizaron. Se obtuvieron 1,35 g de (6-cloro-4-etilpiridazin-3-il)hidrazina en forma del trifluoroacetato y 3,96 g de (6-cloro-5-etilpiridazin-3-il)hidrazina en forma del trifluoroacetato.

(6-Cloro-4-etilpiridazin-3-il)hidrazina en forma del trifluoroacetato, W3.003

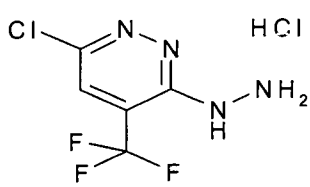
Tr de LC-MS: 0,20 min [M+H$^+$]: 173,1 (met. c)

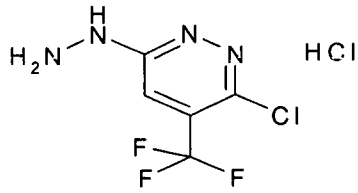
(6-Cloro-5-etilpiridazin-3-il)hidrazina en forma del trifluoroacetato, W3.011

Tr de LC-MS: 0,13 min [M+H$^+$]: 173,1 (met. b)

W3.004 y W3.100

Hidrocloruro de (6-cloro-4-trifluorometil-piridazin-3-il)-hidrazina e hidrocloruro de (6-cloro-5-trifluorometil-piridazin-3-il)-hidrazina





3,6-Dicloro-4-trifluorometilpiridazina (W4.004, 150 mg) se disolvió en dioxano (3 ml) y, después de haber añadido hidrazina monohidrato (100 µl), se agitó a TA. Después de 4 h, el disolvente se separó y el residuo se disolvió en agua/ACN y se separó mediante HPLC preparativa HPLC (met. D). Las fracciones, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo y se liofilizaron. Se obtuvieron 87 mg de hidrocloruro de (6-cloro-4-trifluorometil-piridazin-3-il)-hidrazina y 7 mg de hidrocloruro de (6-cloro-5-trifluorometil-piridazin-3-il)-hidrazina.

Hidrocloruro de (6-cloro-4-trifluorometil-piridazin-3-il)-hidrazina, W3.004

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (NH no listados): 8,27 (1 H)

Tr de LCMS: 0,15 min [M+H$^+$]: 213,1 (met. b)

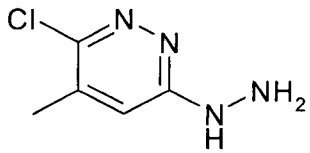
Hidrocloruro de (6-cloro-5-trifluorometil-piridazin-3-il)-hidrazina, W3.100

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (NH no listados): 7,73 (1 H)

Tr de LCMS: 0,37 min [M+H$^+$]: 173,1 (met. c)

W3.005

(6-cloro-5-metilpiridazin-3-il)-hidrazina

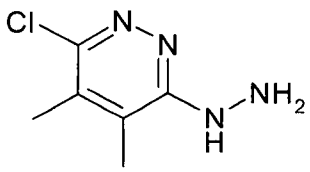


Se sintetizó de forma análoga al documento US 4.578.464

Tr de LC-MS: 0,26 min [M+H$^+$]: 159,1 (met. a)

W3.006

(6-Cloro-4,5-dimetilpiridazin-3-il)hidrazina

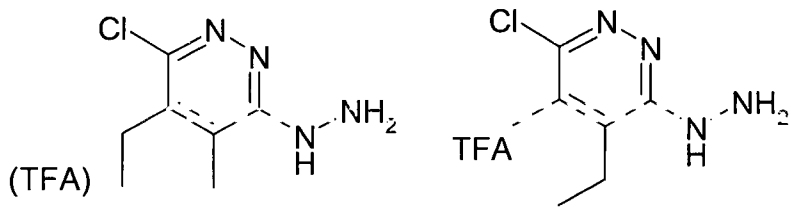


Se mezcló 3,6-dicloro-4,5-dimetilpiridazina (W4.055; 29 g) con 160 ml de una solución de hidrazina monohidrato (160 ml) y se calentó a 90°Cmientras se agitaba durante 4 h. La mezcla de reacción se mezcló con agua y el precipitado se retiró por filtración con succión, se lavó con agua y se secó sobre pentóxido de fósforo. Se obtuvieron 27,2 g del compuesto del título.

Tr de LC-MS: 0,15 min [M+H$^+$]: 173,1 (met. b)

W3.007 y W3.008

(6-Cloro-5-etil-4-metilpiridazin-3-il)hidrazina (en forma de la sal TFA) y sal del ácido trifluoroacético de (6-cloro-4-etil-5-metilpiridazin-3-il)hidrazina



Se cargó inicialmente 3,6-dicloro-4-etil-5-metilpiridazina (W4.008; 1 g) en dioxano (8 ml) con la adición de hidrazina monohidrato (2 ml) en un recipiente para microondas a TA. Después, la mezcla de reacción se mantuvo a 140°C en el microondas durante 1 h. En el transcurso del reposo durante una noche, precipitó un sólido, que se retiró por filtración con succión, se lavó y se secó. Se obtuvieron 345 mg de (6-cloro-5-etil-4-metilpiridazin-3-il)hidrazina en forma de la base libre.

Las aguas madre se concentraron a sequedad y el residuo se purificó por medio de HPLC preparativa (met. F). Las fracciones del producto, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo a presión reducida y se liofilizaron. Se obtuvieron 340 mg de sal del ácido trifluoroacético de 6-cloro-4-etil-5-metilpiridazin-3-il)hidrazina y 239 mg de (6-cloro-5-etil-4-metilpiridazin-3-il)hidrazina en forma del trifluoroacetato.

Sal del ácido trifluoroacético de (6-cloro-5-etil-4-metilpiridazin-3-il)hidrazina, W3.007

Tr de LC-MS: 0,25 min [M+H$^+$]: 187,1 (met. b)

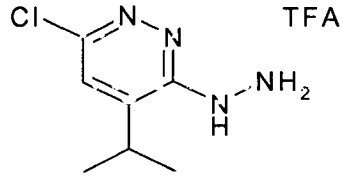
Sal del ácido trifluoroacético de 6-cloro-4-etil-5-metilpiridazin-3-il)hidrazina, W3.008

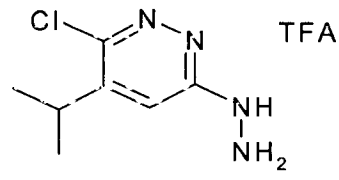
Tr de LC-MS: 0,22 min [M+H$^+$]: 187,1 (met. b)

W3.009 y W3.012

Sal del ácido trifluoroacético de (6-cloro-4-isopropil-piridazin-3-il)-hidrazina y sal del

ácido trifluoroacético de (6-cloro-5-isopropil-piridazin-3-il)-hidrazina





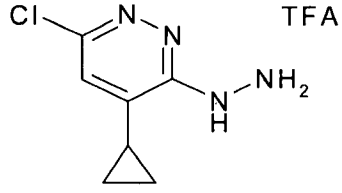
3,6-Dicloro-4-isopropilpiridazina (W4.009; 2,3 g) se convirtió de forma análoga a W3.007 y luego se secó. Después de cromatografía preparativa (met. F), se obtuvieron 260 mg de sal del ácido trifluoroacético de (6-cloro-4-isopropilpiridazin-3-il)hidrazina y 2,16 g de sal del ácido trifluoroacético de (6-cloro-5-isopropilpiridazin-3-il)hidrazina.

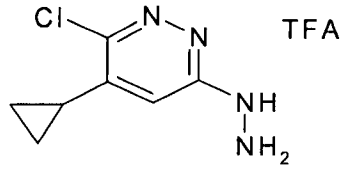
Sal del ácido trifluoroacético de (6-cloro-4-isopropil-piridazin-3-il)-hidrazina, W3.009
Tr de LCMS: 0,20 min [M+H+]: 187,1 (met. b)

Sal del ácido trifluoroacético de (6-cloro-5-isopropil-piridazin-3-il)-hidrazina, W3.012
Tr de LCMS: 0,34 min [M+H+]: 187,1 (met. b)

W3.010 y W3.012

Sal del ácido trifluoroacético de (6-cloro-4-ciclopropil-piridazin-3-il)-hidrazina y sal del ácido trifluoroacético de (6-cloro-5-ciclopropil-piridazin-3-il)-hidrazina





3,6-Dicloro-4-ciclopropilpiridazina (W4.010; 1,4 g) se convirtió de forma análoga a W3.007 y luego se secó. Después de cromatografía preparativa (met. F), se obtuvieron 805 mg de sal del ácido trifluoroacético de (6-cloro-4-ciclopropilpiridazin-3-il)hidrazina y 708 mg de (6-cloro-5-ciclopropilpiridazin-3-il)hidrazina.

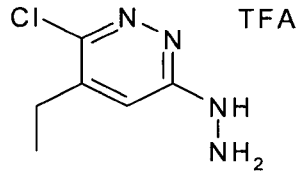
Sal del ácido trifluoroacético de (6-cloro-4-ciclopropil-piridazin-3-il)-hidrazina, W3.010
Tr de LCMS: 0,15 min [M+H+]: 185,1 (met. b)

Sal del ácido trifluoroacético de (6-cloro-5-ciclopropil-piridazin-3-il)-hidrazina, W3.012

Tr de LCMS: 0,22 min [M+H$^+$]: 185,1 (met. b)

W3.011

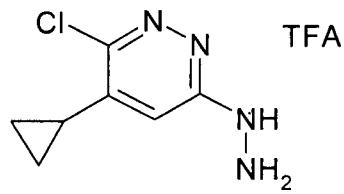
Sal del ácido trifluoroacético de (6-cloro-5-etil-piridazin-3-il)-hidrazina



véase W3.003

W3.012

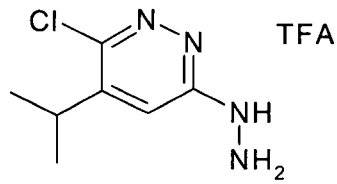
Sal del ácido trifluoroacético de (6-cloro-5-ciclopropil-piridazin-3-il)-hidrazina



véase W3.010

W3.013

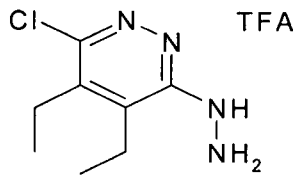
Sal del ácido trifluoroacético de (6-cloro-5-isopropil-piridazin-3-il)-hidrazina



véase W3.009

W3.014

Sal del ácido trifluoroacético de (6-cloro-4,5-dietil-piridazin-3-il)-hidrazina

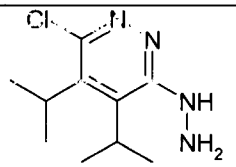
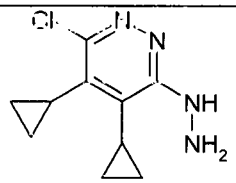


3,6-Dicloro-4,5-dietilpiridazina (W4.014; 3,0 g) se convirtió de forma análoga a

W3.007 y luego se secó. Después de cromatografía preparativa (met. F), se obtuvieron 2,0 g del compuesto del título.

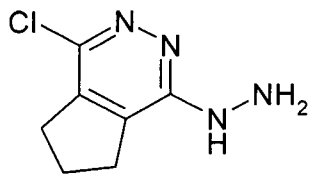
Tr de LCMS: 0,38 min [M+H$^+$]: 201,1 (met. b)

De forma análoga a W3.007, se prepararon:

Número		Tr de LCMS	[M+H$^+$]	Comentario:
W3.015		0,76 min	229,2 (met. b)	W4.015 300 mg; 6 h MO; no se requirió purificación por HPLC; producto: 278 mg
W3.016		0,65 min	225,1 (met. b)	W4.016 500 mg; HPLC(met. B); se hizo alcalino con carbonato potásico y se extrajo; producto: 352 mg

W3.017

(4-Cloro-6,7-dihidro-5H-ciclopenta[d]piridazin-1-il)-hidrazina

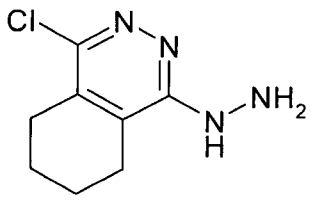


1,4-Dicloro-6,7-dihidro-5H-ciclopenta[d]piridazina (W4.017; 3,89 g) se convirtió, se sometió a tratamiento y se aisló de forma análoga a W3.006. Se obtuvieron 3,24 g del compuesto del título.

Tr de LCMS: 0,20 min [M+H$^+$]: 165,1 (met. b)

W3.018

(4-Cloro-5,6,7,8-tetrahidro-ftalazin-1-il)-hidrazina

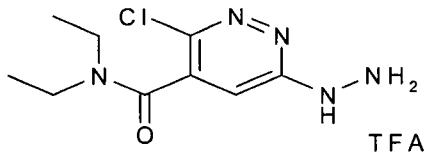


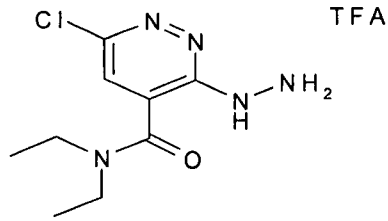
1,4-Dicloro-5,6,7,8-tetrahidroftalazina (W4.018; 10,3 g) se convirtió de forma análoga a W3.006. Sin embargo, después de haber añadido agua, la mezcla se extrajo con DCM, y la fase en DCM se separó, se secó, se filtró y se concentró. Se obtuvieron 9,1 g del compuesto del título.

Tr de LCMS: 0,68 min [M+H$^+$]: 199,1 (met. a)

W3.019 y W3.020

Sal del ácido trifluoroacético de N,N-dietil-3-cloro-6-hidrazinopiridazina-4-carboxamida y sal del ácido trifluoroacético de N,N-dietil-6-cloro-3-hidrazinopiridazina-4-carboxamida





N,N-Dietil-3,6-dicloropiridazina-4-carboxamida (W4.019; 18 g) se suspendió en agua (60 ml) y se mezcló con hidrazina monohidrato (2,8 ml). Después de agitar a 60°C durante 1 h, la mezcla se calentó hasta 100°C durante 2 h. Después de enfriar hasta TA, la mezcla se combinó con DCM y se extrajo cuatro veces con DCM. Los extractos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó mediante HPLC preparativa (met. C). Las fracciones con contenido en producto, limpias se combinaron en cada caso, se liberaron de ACN y se liofilizaron. Se obtuvieron 910 mg de sal del ácido trifluoroacético de N,N-dietil-3-cloro-6-hidrazinopiridazina-4-carboxamida y 560 mg de sal del ácido trifluoroacético de N,N-dietil-6-cloro-3-hidrazinopiridazina-4-carboxamida.

Sal del ácido trifluoroacético de N,N-dietil-3-cloro-6-hidrazinopiridazina-4-carboxamida

Tr de LCMS: 0,79 min [M+H$^+$]: 244,1 (met. a)

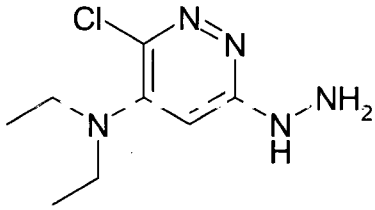
Sal del ácido trifluoroacético de N,N-dietil-6-cloro-3-hidrazinopiridazina-4-carboxamida

W3.020

Tr de LCMS: 0,68 min [M+H$^+$]: 244,1 (met. a)

W3.021

Sal del ácido trifluoroacético de (3-cloro-6-hidrazinopiridazin-4-il)-dietilamina



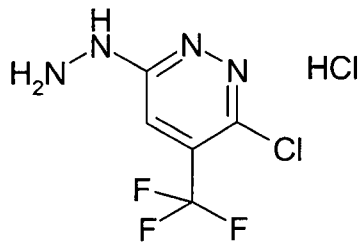
TFA

(3,6-Dicloropiridazin-4-il)dietilamina (W4.021; 500 mg) se cargó inicialmente en dioxano (20 ml) al tiempo que se agitaba, y se mezcló con hidrato de hidrazina (0,65 ml). Después de ello, la mezcla se calentó primeramente a 80°C durante 2 h y luego a reflujo durante 3 h. Después de dejar reposar durante el fin de semana, la mezcla se calentó a reflujo otras 48 h y, después del enfriamiento, se retiró el disolvente. El residuo se purificó mediante HPLC preparativa (met. A). Las fracciones con contenido en producto, limpias se combinaron en cada caso, se liberaron de ACN, se basificaron con solución saturada de hidrógeno-carbonato de sodio y luego se extrajeron cinco veces con EA y cinco veces con DCM. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. Se aislaron 118 mg de reaccionante y 220 mg del compuesto del título.

Tr de LCMS: 1,24 min [M+H$^+$]: 220,1 (met. a)

W3.100

Hidrocloruro de (6-cloro-5-trifluorometil-piridazin-3-il)-hidrazina



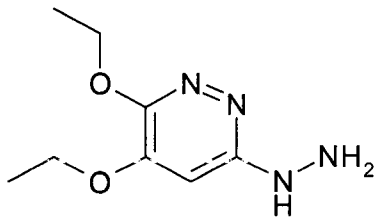
HCl

Véase W3.004

W3.120

(5,6-Dietoxipiridazin-3-il)-hidrazina

000366

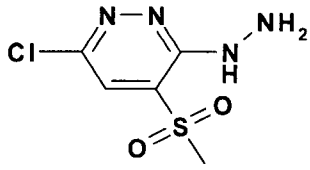


N-(5,6-Dietoxipiridazin-3-il)-N-nitroamina (W4.120; 114 mg) se disolvió en ácido acético (5 ml) y se añadió gota a gota, mientras se enfriaba con hielo y se agitaba a entre 10 y 20°C, a una mezcla de zinc (130 mg) en agua (3 ml). Después de ello, se retiró el baño de hielo y la mezcla se agitó a TA durante 1 h. Luego, la mezcla se alcalinizó con solución de hidróxido de sodio 10 N, la fase acuosa se extrajo tres veces con DCM y las fases en DCM combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó mediante HPLC preparativa (met. A). Las fracciones con contenido en producto, limpias se combinaron en cada caso, se liberaron de ACN, se basificaron con solución saturada de carbonato de potasio y luego se extrajeron tres veces con DCM. Las fases orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. Se obtuvieron 50 mg del compuesto del título.

Tr de LCMS: 0,37 min [M+H$^+$]: 199,2 (met. b)

W3.126

(6-Cloro-4-metanosulfonilpiridazin-3-il)hidrazina

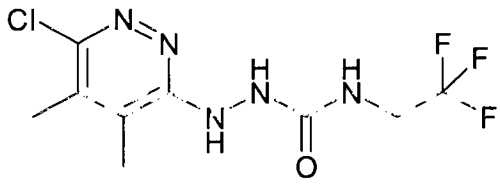


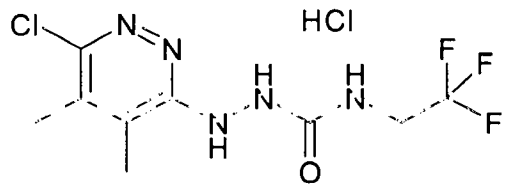
Se disolvió 3,6-dicloro-4-metanosulfonilpiridazina (W4.126; 660 mg, 2,9 mmol) en 1,4-dioxano (5 ml) y se añadió hidrato de hidrazina (295 µl, 5,8 mmol). La mezcla se agitó a TA durante 4 h, después se concentró y el residuo se purificó por cromatografía ultrarrápida (diclorometano:acetato de etilo). Rendimiento: 200 mg

Tr de LC-MS: 0,17 min [M+H$^+$]: 248,0 (met. c)

W3.150

N*-(6-Cloro-4,5-dimetil-piridazin-3-il)-amino-N-(2,2,2-trifluoroetil)-urea e hidrocloruro de N*-(6-cloro-4,5-dimetil-piridazin-3-il)-amino-N-(2,2,2-trifluoroetil)-urea



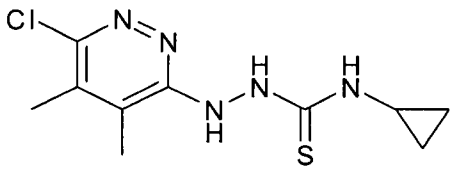


Cloroformiato de 4-nitrofenilo (750 mg) se disolvió en THF (55 ml), se añadió 2,2,2-trifluoroetilamina (0,3 ml) al tiempo que se agitaba y la mezcla se agitó a TA durante 3 h. Luego se añadió (6-cloro-4,5-dimetilpiridazin-3-il)hidrazina (W3.006, 620 mg) disueltos en THF (100 ml), seguido de trietilamina (0,7 ml), y se agitó a TA durante 3 h. Después de dejar reposar durante una noche, el sólido precipitado se separó por filtración con succión y se secó. Se obtuvieron 840 mg de la base libre, que seguía conteniendo cantidades importantes de hidrocloruro de trietilamina. Las aguas madre se secaron y se purificaron mediante HPLC preparativa (met. D). Las fracciones con contenido en producto, limpias se combinaron y secaron. Se obtuvieron 400 mg adicionales del compuesto del título en forma del hidrocloruro.

Tr de LCMS: 0,40 min [M+H$^+$]: 298,1 (met. b)

W3.166

N*-(6-Cloro-4,5-dimetilpiridazin-3-il)amino-N-(ciclopropil)tiourea

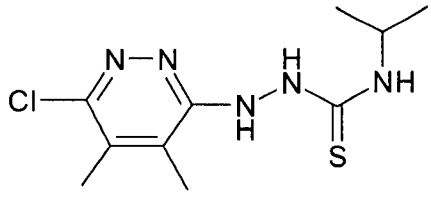


(6-Cloro-4,5-dimetilpiridazin-3-il)hidrazina (W3.006, 540 mg) se disolvió en cloruro de metileno (50 ml) y se añadió isotiocianato de ciclopropilo (290 µl) al tiempo que se agitaba. La mezcla se agitó a TA durante 7 h y luego se dejó reposar durante una noche. Después de ello, se mezcló con dietil-éter (50 ml) y se agitó durante 3 h, y el precipitado formado se separó por filtración con succión. El precipitado se lavó con éter y se secó a presión reducida. Se obtuvieron 830 mg del compuesto del título.

Tr de LCMS: 0,62 min [M+H$^+$]: 272,1 (met. b)

W3.167

N*-(6-Cloro-4,5-dimetilpiridazin-3-il)-amino-N-(isopropil)tiourea

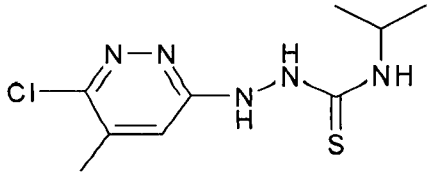


(6-Cloro-4,5-dimetilpiridazin-3-il)hidrazina (W3.006, 330 mg) se hizo reaccionar con isotiocianato de isopropilo (235 µl) y se trató de forma análoga a W3.166. El precipitado obtenido era 428 mg. Las aguas madre se secaron y se purificaron utilizando gel de sílice (cartucho de 70 g, gradiente de 0-30% de DCM/metanol en 30 min). Esto proporcionó 119 mg adicionales de producto.

Tr de LCMS: 0,78 min [M+H$^+$]: 274,1 (met. b)

W3.168

N*-(6-Cloro-5-metilpiridazin-3-il)-amino-N-(isopropil)tiourea

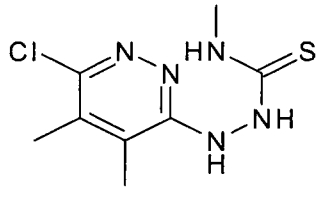


6-Cloro-5-dimetilpiridazin-3-il)hidrazina en forma de la sal del ácido trifluoroacético (W3.005, 660 mg) se disolvió en DCM (55 ml) al tiempo que se agitaba con isotiocianato de isopropilo (258 µl) y se añadió trietilamina (310 ml). El tratamiento y el aislamiento se efectuaron de forma análoga al método descrito en W3.167. En este caso, se aislaron 140 mg del compuesto del título en forma de un precipitado.

Tr de LCMS: 0,81 min [M+H$^+$]: 260,1 (met. b)

W3.169

N'-(4-Cloro-2,3-dimetilfenil)hidrazino-N-metiltiourea



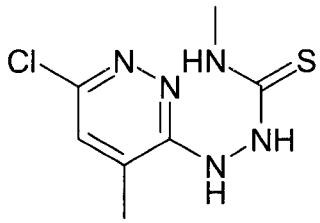
Se disolvió (6-cloro-4,5-dimetilpiridazin-3-il)hidrazina (W3.055; 8,00 g) en DCM (400 ml) y se mezcló con isotiocianato de metilo (3,39 g). Posteriormente, la mezcla se agitó a TA durante 24 h y se dejó en reposo durante el fin de semana. El precipitado

se retiró por filtración, se lavó con DCM y se secó en una vitrina de secado a 45°C. Se obtuvieron 11,25 g del compuesto del título.

Tr de LC-MS: 0,29 min [M+H$^+$]: 246,1 (met. b)

W3.170

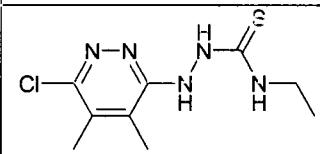
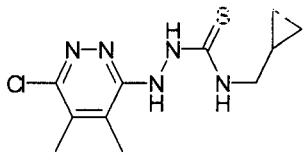
N'-(6-Cloro-4-metilpiridazin-3-il)-amino-N-metiltiourea



(6-Cloro-4-metil-piridazin-3-il)-hidrazina (W3.002; 5,5 g) se hizo reaccionar y se sometió a tratamiento de forma análoga a W3.169. Sin embargo, la agitación se continuó durante tres días en lugar de un día. Se obtuvieron 7,75 g del compuesto del título.

Tr de LCMS: 0,20 min [M+H$^+$]: 232,1 (met. b)

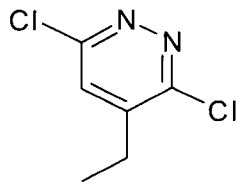
De forma análoga a W3.169, se prepararon:

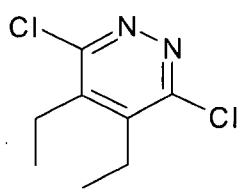
Número		Tr de LCMS	[M+H$^+$]	Comentario:
W3.191		0,50 min	260,0 (met. b)	W3.006 5,0 g; producto: 7,6 g
W3.192		0,64 min	286,0 (met. b)	W3.006 5,0 g; producto: 7,8 g

W4

W4.003 y W4.014

3,6-Dicloro-4-etilpiridazina y 3,6-dicloro-4,5-dietilpiridazina





De forma análoga a: Samaritoni, Org. Prep. Proc. Int. 117 (1988)

Se cargaron inicialmente 3,6-dicloropiridazina (10 g), nitrato de plata (5,7 g) y ácido propiónico (7,5 ml) en agua (125 ml) y, a 50°C, se añadió gota a gota ácido sulfúrico concentrado (11 ml). Después de la adición, la mezcla de reacción se calentó a 60°C y se añadió lentamente gota a gota una solución de amonio persulfato (46 g) en agua (125 ml) durante 20 min. Después de la adición, la mezcla se calentó a 70°C durante 30 min. Después de dejar en reposo durante una noche, la mezcla de reacción se vertió en hielo/agua y se ajustó a un valor de pH de 7 con una solución al 25% de hidróxido de amonio. Después, la mezcla se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. El residuo se purificó por medio de HPLC preparativa (met. C). Las fracciones del producto, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo a presión reducida y se extrajeron tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 6,6 g de 3,6-dicloro-4-etilpiridazina y 3,0 g de 3,6-dicloro-4,5-dietilpiridazina.

3,6-Dicloro-4-etilpiridazina, W4.003

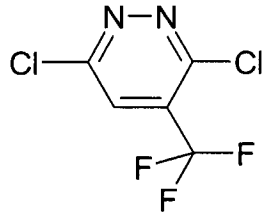
Tr de LC-MS: 0,63 min [M+H$^+$]: 177,1 (met. b)

3,6-Dicloro-4,5-dietilpiridazina, W4.014

Tr de LC-MS: 1,02 min [M+H$^+$]: 205,1 (met. b)

W4.004

3,6-Dicloro-4-trifluorometil-piridazina.



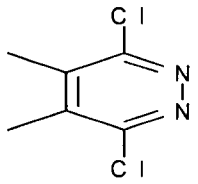
4-Trifluorometil-1,2-dihidropiridazin-3,6-diona (W5.004; 125 mg) se cargó inicialmente en oxicloruro de fósforo (2 ml) en forma de una suspensión al tiempo que se agitaba a TA. Después de ello, la mezcla de reacción se calentó hasta 80°C durante 7 h, luego se añadió pentacloruro de fósforo (100 mg) y la mezcla se agitó

a 80°C durante una noche. Después del enfriamiento, la mezcla se añadió a hielo-agua y la fase acuosa se extrajo tres veces con DCM. Las fases orgánicas combinadas se secaron sobre sulfato de sodio y, después de separar por filtración el desecante, se secaron a presión reducida. Se obtuvieron 150 mg del compuesto del título.

Tr de LCMS: 0,94 min [M+H$^+$]: 217,1 (met. b)

W4.006

3,6-Dicloro-4,5-dimetilpiridazina

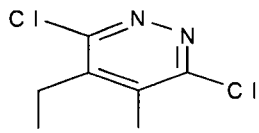


Se suspendió 4,5-dimetil-1,2-dihidropiridazina-3,6-diona (W5.055; 69,7 g) en oxicloruro de fósforo (150 ml) y se calentó a 80°Cdurante 2 h. Después de un periodo de refrigeración, la mezcla se añadió a hielo-agua y se ajusto cuidadosamente a un valor de pH de 10 con NaOH 10 M mientras se enfriaba con hielo. El precipitado se retiró por filtración con succión, se lavó con agua y se secó. Se obtuvieron 78,3 g del compuesto del título.

Tr de LC-MS: 0,63 min [M+H$^+$]: 177,1 (met. b)

W4.007

3,6-Dicloro-4-etil-5-metilpiridazina

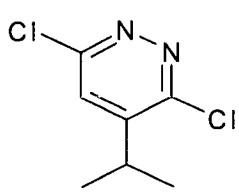
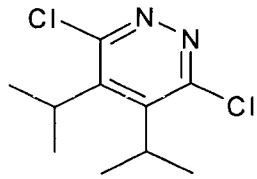


El compuesto se sintetizó de forma análoga a W4.003. El reactivo usado fue 3,6-dicloro-4-metilpiridazina (4 g). Se obtuvieron 3,6 g del compuesto del título.

Tr de LC-MS: 0,92 min [M+H$^+$]: 191,1 (met. b)

W4.009 y W4.015

3,6-Dicloro-4-isopropil-piridazina y 3,6-Dicloro-4,5-diisopropil-piridazina

El compuesto se sintetizó de forma análoga a W4.003. Se utilizaron 2,5 g de 3,6-dicloropiridazina y ácido isobutírico (2,34 ml) para obtener 2,46 g de 3,6-dicloro-4-isopropilpiridazina y 0,33 g de 3,6-dicloro-4,5-diisopropilpiridazina.

3,6-Dicloro-4-isopropil-piridazina, W4.009

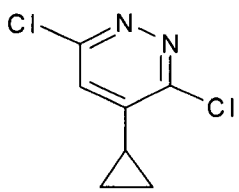
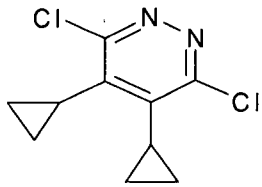
Tr de LCMS: 0,96 min [M+H$^+$]: 191,1 (met. b)

3,6-Dicloro-4,5-diisopropil-piridazina, W4.015

Tr de LCMS: 1,14 min [M+H$^+$]: 233,1 (met. b)

W4.010 y W4.016

3,6-Dicloro-4-ciclopropil-piridazina y 3,6-Dicloro-4,5-diciclopropil-piridazina

El compuesto se sintetizó de forma análoga a W4.003. Se utilizaron 3 g de 3,6-dicloropiridazina y ácido ciclopropanocarboxílico (2,41 ml) para obtener 1,6 g de 3,6-dicloro-4-ciclopropilpiridazina y 0,96 g de 3,6-dicloro-4,5-diciclopropilpiridazina.

3,6-Dicloro-4-ciclopropil-piridazina, W4.010

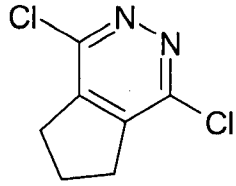
Tr de LCMS: 0,87 min [M+H$^+$]: 189,1 (met. b)

3,6-Dicloro-4,5-diciclopropil-piridazina, W4.016

Tr de LCMS: .1,05 min [M+H$^+$]: 229,1 (met. b)

W4.017

1,4-Dicloro-6,7-dihidro-5H-ciclopenta[d]piridazina

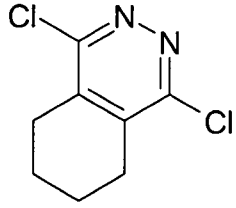


2,3,6,7-Tetrahidro-5H-ciclopenta[d]piridazin-1,4-diona (W5.017; 11,3 g) se suspendió en oxicloruro de fósforo (36,7 ml) y se calentó hasta 80°C durante 2 h. Después de enfriar, la mezcla se añadió a hielo-agua y se ajustó cuidadosamente a pH 10 con NaOH 10 M al tiempo que se enfriaba con hielo, y la fase en agua se extrajo tres veces con EA. Las fases en EA combinadas se secaron, se filtraron y se concentraron. Se obtuvieron 3,89 g del compuesto del título.

Tr de LCMS: 0,71 min [M+H$^+$]: 189,1 (met. b)

W4.018

1,4-Dicloro-5,6,7,8-tetrahidro-ftalazina

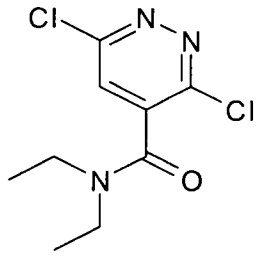


2,3,5,6,7,8-Hexahidroftalazina-1,4-diona (W5.018; 10,1 g) se preparó de forma análoga a W4.006. Sin embargo, el precipitado se purificó subsiguientemente utilizando gel de sílice (300 g, n-heptano/EA 7:3). Se obtuvieron 10,32 g del compuesto del título.

Tr de LCMS: 1,29 min [M+H$^+$]: 203,1 (met. a)

W4.019

Dietilamida del ácido 3,6-dicloro-piridazina-4-carboxílico



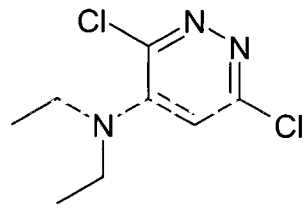
Cloruro de 3,6-dicloropiridazina-4-carbonilo (2,5 g) se cargó inicialmente en DCM (25 ml) a TA. Después de ello, se añadió lentamente, gota a gota y al tiempo que se

agitaba, dietilamina (1,5 ml) predisuelta en DCM (5 ml). Después de agitar a TA durante 3 h, la mezcla se combinó con agua y se extrajo tres veces con DCM. Las fases en DCM combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó mediante gel de sílice (cartucho de 70 g gradiente de n-heptano/EA). Se obtuvieron 1,8 g del compuesto del título.

Tr de LCMS: 0,97 min [M+H$^+$]: 248,1 (met. a)

W4.021

(3,6-Dicloro-piridazin-4-il)-dietil-amina

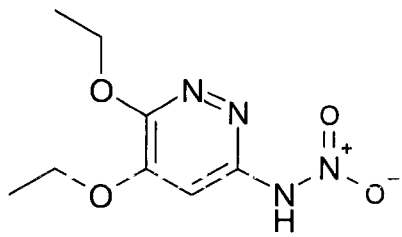


3,4,6-Tricloropiridazina (2 g) y dietilamina (2,4 ml) se cargaron inicialmente en tolueno (10 ml) y se dejaron reposar a TA durante 3 días. Luego, la mezcla se combinó con agua y EA, y la fase en EA se separó. La fase en EA se lavó tres veces con agua, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 70 g, gradiente de 0-50% de n-heptano/EA en 60 min). Se obtuvieron 1,1 g del compuesto del título.

Tr de LCMS: 1,24 min [M+H$^+$]: 248,1 (met. a)

W4.120

N-(5,6-Dietoxipiridazin-3-il)-N-nitroamina



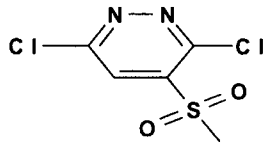
5,6-Dietoxipiridazin-3-ilamina (análogamente a T. Horie en Chemical & Pharmaceutical Bulletin (1963), 11(9), 1157-67; 160 mg) se cargó inicialmente, disuelta en ácido sulfúrico concentrado (4 ml) a TA. La mezcla se enfrió luego hasta 0°C y se añadieron, gota a gota, 2 ml de una mezcla 1:1 de ácido nítrico concentrado y ácido sulfúrico concentrado. Al cabo de 20 min a 0°C, se retiró el baño de hielo y la mezcla se agitó durante 4 h. Luego se enfrió de nuevo hasta 0°C,

se añadieron 0,5 ml adicionales de la mezcla de ácidos y la mezcla se agitó a 0°C durante otra hora. Luego se mezcló con hielo al tiempo que se enfriaba con hielo.Después de añadir DCM, las fases se separaron y extrajeron tres veces con DCM. Las fases en DCM combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron.Se obtuvieron 188 mg del compuesto del título.

Tr de LCMS: 0,81 min [M+H$^+$]: 236,2 (met. b)

W4.126

3,6-Dicloro-4-metanosulfonilpiridazina



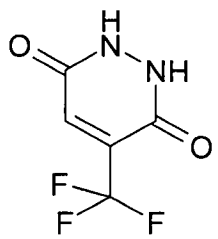
Se agitaron 3,4,6-tricloropiridazina (2,5 g; 13,6 mmol) y sal sódica del ácido metanosulfínico (2,78 g, 27,26 mmol) en 20 ml de un disolvente mezcla de agua/THF/DMF (5:10:5) a TA durante 30 h. El disolvente se retiró a presión reducida y el residuo se repartió entre acetato de etilo y una solución saturada de cloruro de amonio. La fase orgánica se retiró y se concentró y el producto en bruto se purificó por cromatografía ultrarrápida (diclorometano:metanol). Rendimiento: 1,4 g

Tr de LC-MS: 0,44 min [M+H$^+$]: 227,0 (met. b)

W5

W5.004

4-Trifluorometil-1,2-dihidro-piridazina-3,6-diona



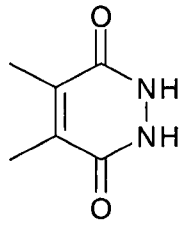
Se introdujo en porciones 3-trifluorometilfuran-2,5-diona (5 g) a una solución ya en ebullición de dihidrocloruro de hidrazina (3,2 g) en agua (50 ml). Después de agitar durante 4 h, la mezcla se dejó en reposo durante una noche; al día siguiente, el calentamiento a reflujo se continuó durante 8 h y la mezcla se sometió a reflujo durante otras 8 h y se dejó en reposo durante una noche. Después, se secó y el residuo se purificó por medio de cromatografía preparativa (met. C). Las fracciones

puras se combinaron, el ACN se separó y el residuo se liofilizó. Se obtuvieron 250 mg del compuesto del título.

Tr de LCMS: 0,23 min [M+H$^+$]: 181,1 (met. b)

W5.006

4,5-Dimetil-1,2-dihidropiridazina-3,6-diona

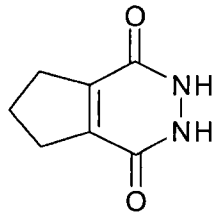


Se disolvió dihidrocloruro de hidrazina (83,6 g) en agua (20 ml), se calentó a 100°C y se introdujo 3,4-dimetilfuran-2,5-diona (100,4 g) mientras se agitaba. Después, la mezcla se calentó a reflujo durante 3 h. Posteriormente, el precipitado formado se retiró por filtración con succión, se lavó con agua y se secó. El residuo se suspendió en EA (2 l) y después el EA se retiró por filtración con succión. El residuo se secó. Se obtuvieron 69,7 g del compuesto del título.

Tr de LC-MS: 0,19 min [M+H$^+$]: 141,1 (met. b)

W5.017

2,3,6,7-Tetrahidro-5H-ciclopenta[d]piridazina-1,4-diona

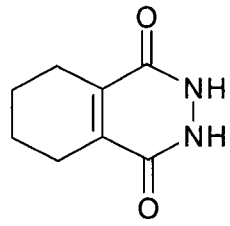


Se hizo reaccionar 5,6-dihidro-4H-ciclopenta[c]furan-1,3-diona (11,3 g) y se trató de forma análoga a W5.006. No se realizó la suspensión en EA. Se obtuvieron 11.3 g de producto en bruto.

Tr de LCMS: 0,19 min [M+H$^+$]: 153,1 (met. b)

W5.018

2,3,5,6,7,8-Hexahidro-ftalazina-1,4-diona



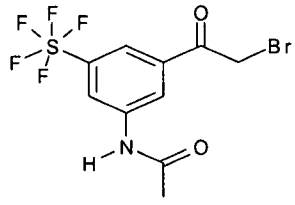
Se hizo reaccionar 2,3,5,6,7,8-hexahidro-ftalazina-1,4-diona (10,0 g) de forma análoga a W5.017. Se obtuvieron 10,14 g del compuesto del título.

Tr de LCMS: 0,72 min [M+H$^+$]: 167,1 (met. a)

Síntesis de las unidades de la "mitad oriental"

O1.001

N-[3-(2-Bromoacetil)-5-(pentafluorosulfanil)fenil]acetamida

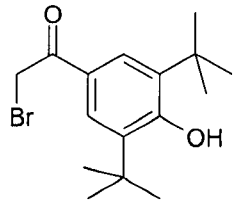


Se disolvió N-[3-acetil-5-(pentafluorosulfanil)fenil]acetamida (859 mg, para la preparación, véase el ejemplo 1) en una mezcla de metanol (10 ml) y THF (10 ml) y se añadió en porciones tribromuro de feniltrimetilamonio (1,065 g) mientras se agitaba. Después de agitar a TA durante 2 h, la mezcla se calentó a 40°C durante 3 h más. Después de un periodo de refrigeración, la mezcla de reacción se añadió a ácido sulfúrico 2 N y la fase acuosa se extrajo 3 veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron. El producto en bruto se purificó usando gel de sílice con acetato de etilo/heptano como eluyente. Se obtuvieron 480 mg del compuesto deseado.

Tr de LC-MS: 1,47 min [M+H$^+$]: 382,0 (met. a)

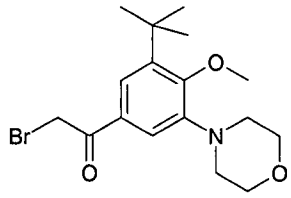
O1.002

2-Bromo-1-(3,5-di-terc-butil-4-hidroxifenil)etanona (Apollo Scientific)



O1.003

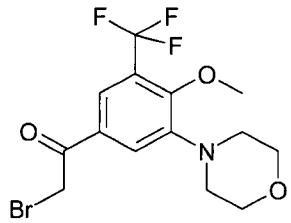
2-Bromo-1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)etanona



Se preparó como se describe en el documento WO 2004/078721.

O1.004

2-Bromo-1-(4-metoxi-3-morfolin-4-il-5-trifluorometilfenil)etanona

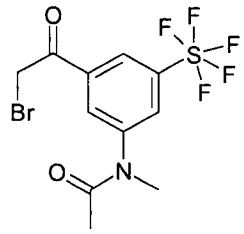


Se disolvió 4-[5-(1,1-dimetoxietil)-2-metoxi-3-trifluormetilfenil]morfolina (O2.004; 460 mg) en una mezcla de metanol (1,4 ml) y THF (4 ml), la mezcla se enfrió a 7°C y se añadió en porciones tribromuro de feniltrimetilamonio (530 mg) mientras se agitaba. Después de agitar a TA durante 3 h, la mezcla se dejó en reposo durante una noche. Después, se añadieron una solución acuosa de tiosulfato (0,8 ml; p = 5%) y agua (4 ml) y la mezcla se mezcló con EA y se extrajo tres veces con EA. Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se disolvió en una mezcla de acetonitrilo (20 ml) y agua (0,5 ml) y se mezcló con TFA (0,5 ml) mientras se agitaba. Después de agitar a TA durante 5 h, el disolvente se retiró y el residuo se mezcló con agua, se neutralizó con una solución saturada de hidrógeno-carbonato sódico y se extrajo tres veces con acetato de etilo. Los extractos combinados se secaron sobre magnesio, se filtraron y se concentraron. El producto en bruto se purificó usando gel de sílice con acetato de etilo/heptano como eluyente. Se obtuvieron 200 mg del compuesto deseado.

Tr de LC-MS: 1,67 min [M+H$^+$]: 382,0 (met. a)

O1.005

N-[3-(2-Bromoacetil)-5-pentafluorosulfanilfenil]-N-metilacetamida

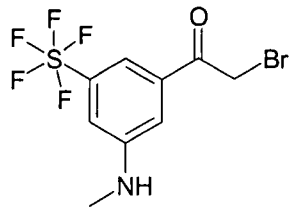


Se disolvió 2-bromo-1-[3-metilamino-5-(pentafluorosulfanil)fenil]etanona (O1.006; 100 mg) en DCM (5 ml) y se añadió bromuro de acetilo (21 µl) mientras se agitaba. Después de agitar a TA durante 4 h, se añadió más cantidad de bromuro de acetilo (21 µl) y la mezcla se agitó adicionalmente a TA. Después de dejar en reposo durante una noche, la mezcla se mezcló de nuevo una vez con bromuro de acetilo (21 µl) y se agitó durante 2 h. Después, la mezcla de reacción se concentró y el residuo se purificó por medio de HPLC preparativa (met. A). Las fracciones del producto, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo a presión reducida, se ajustaron a un valor de pH de 9 con una solución de hidrogenocarbonato sódico y se extrajeron tres veces con EA. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se aislaron 50 mg del compuesto del título y 18 mg de reactivo.

Tr de LC-MS: 1,47 min [M+H$^+$]: 396,0 (met. a)

O1.006

2-Bromo-1-[3-metilamino-5-(pentafluorosulfanil)fenil]etanona



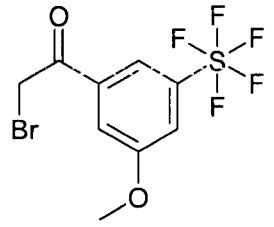
Se mezcló N-[3-(2-bromoacetil)-5-(pentafluorosulfanil)fenil]-2,2,2-trifluoro-N-metilacetamida (O1.075; 1,2 g) con agua (15 ml) y se añadió gota a gota ácido sulfúrico concentrado (15 ml) mientras se agitaba y se enfriaba con hielo. La mezcla se calentó a 80°C y se agitó a esta temperatura durante 7 h. Después de un periodo de refrigeración, la mezcla de reacción se añadió lentamente a una mezcla de una solución 10 N de hidróxido sódico y EA y la fase acuosa se extrajo cinco veces con EA. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y, después de que el desecante se retirara por filtración, se secaron a presión

reducida. El residuo se purificó por medio de HPLC preparativa (met. A). Las fracciones del producto, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo a presión reducida, se neutralizaron con hidrogenocarbonato sódico y se extrajeron tres veces con EA. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 420 mg del compuesto del título.

Tr de LC-MS: 1,64 min [M+H$^+$]: 354,0 (met. a)

O1.007

2-Bromo-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona

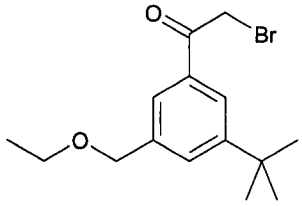


Se disolvió 1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona (O2.007; 1,63 g) en THF (150 ml) y se añadió tribromuro de feniltrimetilamonio (2,2 g) a TA mientras se agitaba. Después de agitar a TA durante 2 h, la mezcla se mezcló con agua, se neutralizó con una solución de hidrogenocarbonato sódico y se extrajo tres veces con EA. La fase de agua alcalina se extrajo 3 veces con EA. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y, después de que el desecante se retirara por filtración, se secaron a presión reducida. El residuo se purificó por medio de HPLC preparativa (met. A). Las fracciones del producto, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo a presión reducida, se neutralizaron con hidrogenocarbonato sódico y se extrajeron tres veces con EA. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se aislaron 1,27 g del compuesto del título.

Tr de LC-MS: 1,65 min [M+H$^+$]: 354,9 (met. b)

O1.008

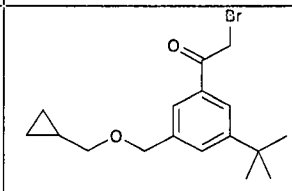
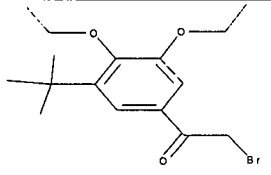
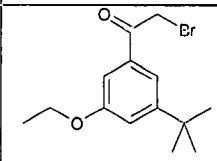
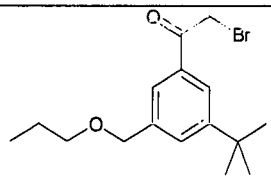
2-Bromo-1-(3-terc-butil-5-etoximetilfenil)etanona

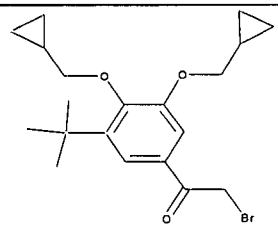


Se disolvió 1-(3-terc-butil-5-etoximetilfenil)etanona (O2.008; 550 mg) en metanol/THF (10 ml/10 ml), se mezcló con tribromuro de feniltrimetilamonio (882 mg) mientras se agitaba y se agitó a TA durante 2 h. Posteriormente, la mezcla de reacción se vertió en DCM (200 ml) y se lavó minuciosamente una vez con una solución al 5% de tiosulfato sódico y una vez con agua. Después, la fase de DCM se secó y se concentró. El residuo se purificó usando gel de sílice (cartucho de 40 g, gradiente de 0-50% de n-heptano/EA en 30 min). Se obtuvieron 566 mg del compuesto del título.

Tr de LC-MS: 1,83 min [M+H$^+$]: 313,2 (met. a)

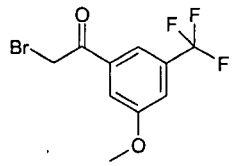
Los siguientes se prepararon de manera análoga:

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
O1.009		1,92 min	339,2 (met. a)	O2.009; 595 mg; producto: 691 mg
O1.010		2,01 min	343,2 (met. a)	O2.010; 410 mg; producto: 405 mg
O1.011		1,77 min	299,2 (met. a)	O2.011; 390 mg; se añadió una solución al 5% de ácido cítrico en lugar de tiosulfato; producto: 387 mg
O1.012		1,94 min	327,2 (met. a)	O2.012; 333 mg; se agitó a TA durante 12 h; se agitó con una solución al 20% de ácido cítrico en lugar de una solución de tiosulfato 1

				h; producto: 327 mg
O1.013		2,16 min	395,3 (met. a)	O2.013; 540 mg; después de la solución de tiosulfato, se lavó adicionalmente con una solución al 20% de ácido cítrico; producto: 600 mg

O1.014

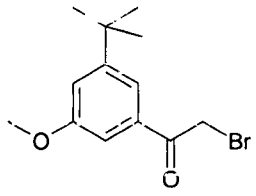
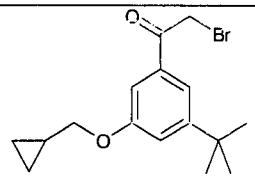
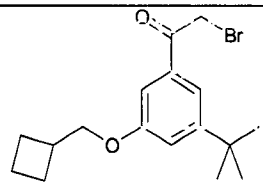
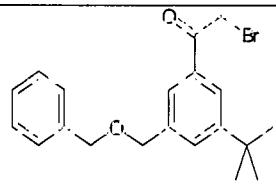
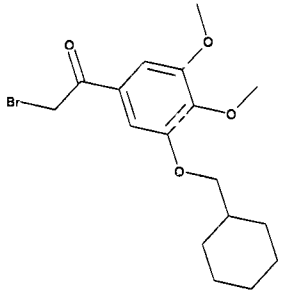
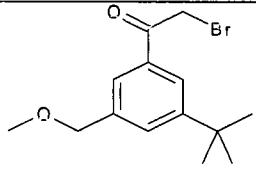
2-Bromo-1-(3-metoxi-5-trifluorometilfenil)etanona



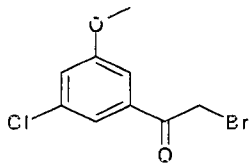
Se disolvió 1-(3-metoxi-5-trifluormetilfenil)etanona (O2.014, 50 mg) en DCM (0,8 ml) y se añadió gota a gota a TA a una mezcla de bromuro de cobre (II) (102 mg) en EA (1,2 ml). Después de calentar a TA durante 2 h, la mezcla se dejó en reposo durante una noche, después la mezcla de reacción se filtró a través de "Celite" y se lavó minuciosamente con EA y el filtrado se secó. El residuo se recogió con EA y una solución semisaturada de hidrogenocarbonato sódico y después se extrajo dos veces con EA. Las fases de EA combinadas se lavaron con una solución semisaturada de hidrogenocarbonato sódico, se secaron sobre sulfato sódico, se filtraron y se concentraron. El producto en bruto se purificó por medio de HPLC preparativa (met. A). Las fracciones del producto, cada una de ellas limpia, se combinaron, se liberaron del acetonitrilo a presión reducida y se extrajeron tres veces con EA. Las fases orgánicas combinadas se secaron sobre sulfato sódico y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 39 mg del compuesto del título.

Tr de LC-MS: 1,64 min [M+H$^+$]: 297,0 (met. a)

Los siguientes se prepararon de forma análoga a O1.008:

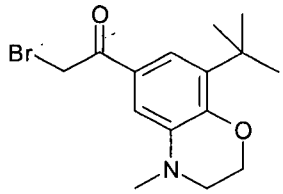
Número		Tr de LC-MS	$[M+H^+]$:	Comentario:
O1.015		1,77 min	285,1 (met. a)	O2.015; 880 mg; se añadió una solución al 5% de ácido cítrico en lugar de una solución de tiosulfato; producto: 327 mg
O1.016		1,97 min	325,1 (met. a)	O2.016; 1,02 g, se agitó con una solución al 5% de ácido cítrico durante 2 h en lugar de una solución de tiosulfato; producto: 1,23 g
O1.017		2,14 min	339,2 (met. a)	O2.017; 25 mg; se agitó con una solución al 5% de ácido cítrico durante 2 h en lugar de una solución de tiosulfato; producto: 314 mg
O1.018		2,18 min	389,3 (met. a)	O2.018; 638 mg; se agitó con una solución al 5% de ácido cítrico durante 2 h en lugar de una solución de tiosulfato; producto: 809 mg
O1.019		1,94 min	371,3 (met. a)	O2.019; 360 mg; después de la solución de tiosulfato, se lavó adicionalmente con una solución al 20% de ácido cítrico; producto: 261 mg
O1.020		1,72 min	299,1 (met. a)	O2.020; 1,53 g, después de la solución de tiosulfato, se lavó adicionalmente con una solución al 20% de ácido cítrico; producto: 1,04 g

000384

O1.021		1,58 min	262,9/ 265,0 (met. a)	O2.021; 2,41 g, después de la solución de tiosulfato, se lavó adicionalmente con una solución al 20% de ácido cítrico; producto: 572 mg

O1.022

2-Bromo-1-(8-terc-butil-4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-6-il)etanona

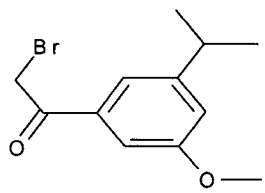


Se calentó 1-(8-terc-dutil-4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-6-il)etanona (250 mg, adquirida en Chembiotek, India) de 50°C a 55°C en una mezcla de ácido acético (4 ml) y tolueno (8 ml). A esta temperatura, se añadió cuidadosamente gota a gota bromo (200 mg disuelto en ácido acético). Después de 2,5 h, el calentamiento se retiró, y la mezcla se mezcló a TA con hielo-agua y se extrajo tres veces con tolueno. Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. El producto en bruto se purificó usando gel de sílice, para obtener 65 mg del compuesto deseado, así como 43 mg más de producto que estaba ligeramente contaminado y 37 mg de reactivo.

Tr de LC-MS: 1,81 min [M+H$^+$]: 326,0 (met. a)

O1.030

2-Bromo-1-(3-isopropil-5-metoxi-fenil)-etanona



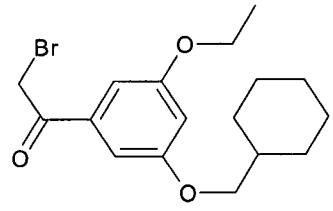
1-(3-Isopropil-5-metoxifenil)etanona (O2.030; 425 mg) se disolvió en metanol/THF (15 ml/15 ml) y se mezcló, al tiempo que se agitaba, con tribromuro de feniltrimetilamonio (831 mg). Después de agitar a TA durante 3 h, la mezcla de reacción se añadió a 50 ml de ácido clorhídrico al 20% y se agitó durante 1 h. Después de añadir agua y EA, la fase en EA se separó, se secó y se concentró. El residuo se disolvió en acetonitrilo (50 ml), y se añadió ácido sulfúrico 2 N (15 ml) a

la solución. Después de dejar en reposo a TA durante 2 h, la mezcla se combinó con agua y se extrajo con EA. La fase en EA se lavó con solución saturada de hidrógeno-carbonato de sodio, se secó y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 40 g, gradiente de 0-50% de n-heptano/EA en 30 min). Se obtuvieron 520 mg del compuesto del título.

Tr de LC-MS: 1,65 min [M+H$^+$]: 271,1 (met. a)

O1.031

2-Bromo-1-(3-ciclohexilmetoxi-5-etoxi-fenil)-etanona

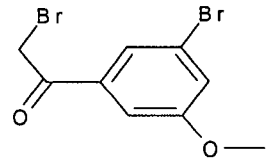


Partiendo de 1-(3-ciclohexilmetoxi-5-etoxi-fenil)-etanona (O2.031, 1,76 g), el compuesto del título se preparó de forma análoga a O1.008. Sin embargo, para la purificación adicional, la cromatografía sobre gel de sílice fue seguida de una etapa de purificación adicional por medio de HPLC preparativa. Se obtuvieron 370 mg del compuesto del título.

Tr de LC-MS: 2,11 min [M+H$^+$]: 355,1 (met. a)

O1.032

2-Bromo-1-(3-bromo-5-metoxi-fenil)-etanona



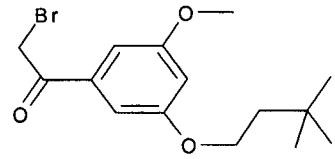
Se disolvió 1-(3-bromo-5-metoxi-fenil)-etanona (O2.032, 1,45 g) en metanol/THF (40 ml/40 ml) y mientras se agitaba se mezcló con tribromuro de feniltrimetilamonio (2,38 g). Después de agitar durante 24 h a TA se añadieron agua y EA. La fase de EA se separó, se secó y se concentró. El residuo se disolvió en acetonitrilo (50 ml) y a la solución se le añadió ácido sulfúrico 2 N (15 ml). Después de dejar en reposo durante 1 h a TA, la mezcla se combino con agua y se extrajo dos veces con EA. La fase en EA se lavó con una solución saturada de hidrógeno-carbonato sódico, se secó y se concentró. El residuo se purificó usando gel de sílice (cartucho de 40 g, gradiente de 0-50% de n-heptano/EA en 30 min). Se obtuvieron

1,39 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,71 (1 H), 7,48 (2 H), 4,97 (2 H), 3,84 (3 H)

O1.033

2-Bromo-1-[3-(3,3-dimetil-butoxi)-5-metoxi-fenil]-etanona

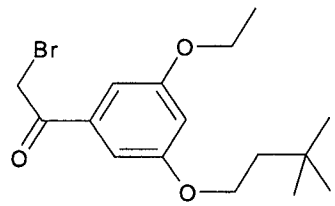


Partiendo de 1-[3-(3,3-dimetil-butoxi)-5-metoxi-fenil]-etanona (1,11 g), el compuesto del título se preparó de forma análoga a O1.031. Se obtuvieron 127 mg del compuesto del título.

Tr de LC-MS: 1,89 min [M+H$^+$]: 329,1 (met. a)

O1.034

2-Bromo-1-[3-(3,3-dimetil-butoxi)-5-etoxi-fenil]-etanona

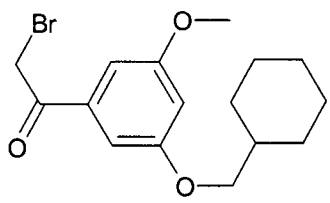


Partiendo de 1-[3-(3,3-dimetil-butoxi)-5-etoxi-fenil]-etanona (950 mg), el compuesto del título se preparó de forma análoga a O1.031. Se obtuvieron 236 mg del compuesto del título, que estaba ligeramente contaminado.

Tr de LC-MS: 2,06 min [M+H$^+$]: 343,2 (met. a)

O1.035

2-Bromo-1-(3-ciclohexilmetoxi-5-metoxi-fenil)-etanona

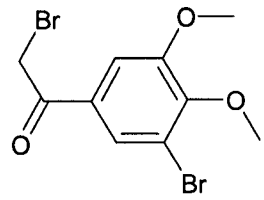


1-(3-ciclohexilmetoxi-5-metoxi-fenil)-etanona (O2.035; 1,33 g) se convirtió de forma análoga a O1.032. Pero en lugar de agitar durante 24 h la mezcla sólo se agitó durante 3 h a TA. Se obtuvieron 950 mg del compuesto del título.

Tr de LC-MS: 2,03 min [M+H$^+$]: 341,2 (met. a)

O1.040

2-Bromo-1-(3-bromo-4,5-dimetoxi-fenil)-etanona

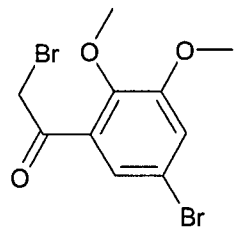


1-(3-bromo-4,5-dimetoxi-fenil)-etanona (O2.040; 1,22 g) se convirtió de forma análoga a O1.032. Se obtuvieron 1,05 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,36 (1 H), 7,58 (1 H), 4,96 (2 H), 3,90 (3 H), 3,82 (3 H)

O1.041

2-Bromo-1-(5-bromo-2,3-dimetoxi-fenil)-etanona

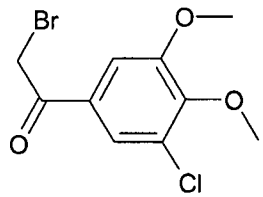


1-(5-bromo-2,3-dimetoxi-fenil)-etanona (O2.041; 1,1 g) se convirtió de forma análoga a O1.032. Se obtuvieron 1,21 g del compuesto del título.

Tr de LC-MS: 1,62 min [M+H$^+$]: 337,0 (met. a)

O1.042

2-Bromo-1-(3-cloro-4,5-dimetoxi-fenil)-etanona

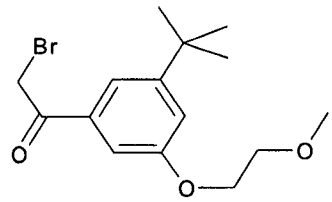


1-(3-cloro-4,5-dimetoxi-fenil)-etanona (O2.042; 490 mg) se convirtió de forma análoga a O1.032. Se obtuvieron 577 mg del compuesto del título.

Tr de LC-MS: 1,54 min [M+H$^+$]: 293,0 (met. a)

O1.043

2-Bromo-1-[3-terc-butil-5-(2-metoxietoxi)fenil]etanona

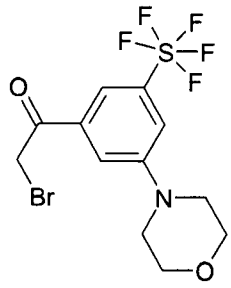


Se disolvió 1-[3-terc-butil-5-(2-metoxietoxi)fenil]etanona (O2.043; 1 g) en metanol/THF (25 ml/25 ml), se mezcló con tribromuro de feniltrimetilamonio (882 mg) mientras se agitaba y se agitó a TA durante una noche. Después, se añadieron 50 ml de una solución al 20% de ácido cítrico y la mezcla se agitó durante 1 h. Posteriormente, se añadió DCM (200 ml) y la mezcla se extrajo tres veces con DCM. Después, las capas de DCM combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó usando gel de sílice (cartucho de 40 g, gradiente de 0-30% de n-heptano/EA en 30 min). Se obtuvieron 1,31 g del compuesto del título.

Tr de LC-MS: 1,72 min [M+H$^+$]: 329,2 (met. a)

O1.044

2-Bromo-1-[3-morfolin-4-il-5-(pentafluorosulfanil)-fenil]-etanona

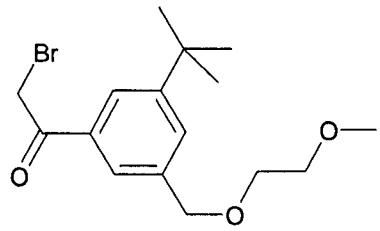


1-[3-Morfolin-4-il-5-(pentafluorosulfanil)fenil]etanona (O2.044; 1,1 g) se disolvió en metanol/THF (20/20 ml) y se mezcló, al tiempo que se agitaba, con bromuro de feniltrimetilamonio (1,25 g). Después de agitar a TA durante 27 h, se añadieron 50 ml de ácido cítrico al 20% y la mezcla se agitó durante 1 h. Después de añadir DCM (100 ml), la fase en DCM se separó, se secó y se concentró. El residuo se disolvió en acetonitrilo (100 ml), y se añadió ácido sulfúrico 2 N (20 ml) a la solución. Después de agitar a TA durante 24 h, la mezcla se combinó con agua y se extrajo con EA. La fase en EA se lavó con solución saturada de hidrógeno-carbonato de sodio, se secó y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 80 g, gardienet de 0-60% de n-heptano/EA en 40 min). Se obtuvieron 866 mg del compuesto del título.

Tr de LC-MS: 1,69 min [M+H$^+$]: 410,0 (met. a)

O1.045

2-Bromo-1-[3-terc-butil-5-(2-metoxi-etoximetil)-fenil]-etanona

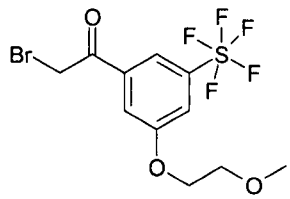


Se hizo reaccionar 1-[3-terc-butil-5-(2-metoxi-etoximetil)-fenil]-etanona (O2.045, 508 mg) de forma análoga a O1.032. Se obtuvieron 470 mg del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,91 (1 H), 7,76 (1 H), 7,66 (1 H), 4,96 (2 H), 4,56 (2 H), 3,58 (2 H), 3,50 (2 H), 3,26 (3 H), 1,32 (9 H)

O1.050

2-Bromo-1-[3-(2-metoxi-etoxi)-5-(pentafluorosulfanil)-fenil]-etanona

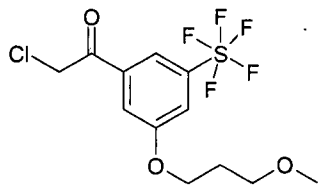


Se hizo reaccionar 1-[3-(2-metoxi-etoxi)-5-(pentafluorosulfanil)-fenil]-etanona (O3.050, 578 mg) de forma análoga a O1.032. Se obtuvieron 290 mg del compuesto del título.

Tr de LC-MS: 1,70 min [M+H$^+$]: 399,0 (met. a)

O1.051

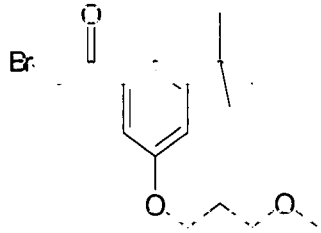
2-Cloro-1-[3-(3-metoxi-propoxi)-5-(pentafluorosulfanil)-fenil]-etanona



Se disolvió 1-[3-(3-metoxi-propoxi)-5-(pentafluorosulfanil)-fenil]-etanona (O2.051; 670 mg) en metanol/THF (10 ml/10 ml) y mientras se agitaba se añadió tribromuro de feniltrimetilamonio (753 mg). Después de agitar durante 24 h a TA se añadieron agua y EA. La fase de EA se separó, se secó y se concentró. El residuo se disolvió

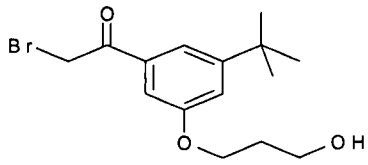
en acetonitrilo (50 ml) y a la solución se le añadió ácido clorhídrico 2 N (15 ml). Después de agitar durante 1 h a TA, se añadió agua y la fase acuosa se extrajo dos veces con EA. La fase de EA se secó, se filtró y se concentró. El residuo se purificó usando gel de sílice (cartucho de 40 g, gradiente de 0-30% de n-heptano/EA en 30 min). Se obtuvieron 722 mg del compuesto del título, que contenía el derivado de bromo análogo como una impureza.

Tr de LC-MS: 1,11 min [M+H$^+$]: 369,0 (met. b)

Número		Tr de LC-MS	[M+H$^+$]	Comentario:
O1.052		1,82 min	343,1 (met. a)	Preparación análoga a O1.013: O2.052; 880 mg; cromatografía: cartucho de 80 g, n-heptano /MtB éter al 0-30% en 60 min; producto: 629 mg

O1.059

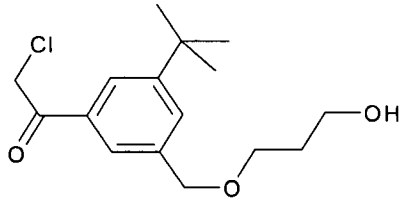
2-Bromo-1-[3-terc-butil-5-(3-hidroxi-propoxi)-fenil]-etanona



Tr de LC-MS: 2,57 min [M+H$^+$]: 329,1 (met. e)

O1.060

1-[3-terc-Butil-5-(3-hidroxi-propoximetil)-fenil]-2-cloro-etanona



Se hizo reaccionar 1-{3-terc-butil-5-[3-(tetrahidro-piran-2-iloxi)-propoximetil]-fenil}-etanona (O2.060; 1,75 g) de forma análoga a O1.063. Se obtuvieron 455 mg del

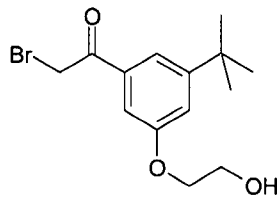
000389
000391

compuesto del título.

Tr de LC-MS: 1,47 min [M+H$^+$]: 299,1 (met. a)

O1.061

2-Bromo-1-[3-terc-butil-5-(2-hidroxi-etoxi)-fenil]-etanona

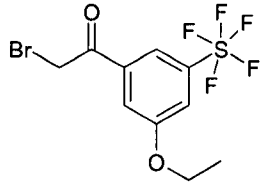


1-{3-terc-Butil-5-[2-(tetrahidropiran-2-iloxi)etoxi]fenil}etanona (O2.061; 3,9 g) se disolvió en metanol/THF (60 ml/60 ml) y se mezcló, al tiempo que se agitaba, con tribromuro de feniltrimetilamonio (5,03 g). Después de agitar a TA durante 3 h, la mezcla de reacción se añadió a ácido cítrico al 20% y se agitó durante 1 h. Después de añadir EA, la fasse en EA se separó, se secó y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 80 g, gradiente de 0-50% de n-heptano/EA en 60 min). Se obtuvieron 2,56 g del compuesto del título.

Tr de LC-MS: 0,90 min [M+H$^+$]: 315,0 (met. b)

O1.062

2-Bromo-1-[3-etoxi-5-(pentafluorosulfanil)-fenil]-etanona

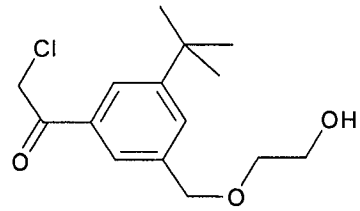


1-[3-Etoxi-5-(pentafluorosulfanil)fenil]etanona (O2.062; 2,24 g) se convirtió de forma análoga a O1.008. La purificación utilizando gel de sílice se realizó como sigue: (cartucho de 120 g, gradiente de 0.20% de n-heptano/MtB-éter en 60 min). Se obtuvieron 2,07 g del compuesto del título.

Tr de LC-MS: 1,83 min [M+H$^+$]: 368,9 (met. a)

O1.063

1-[3-terc-Butil-5-(2-hidroxi-etoximetil)-fenil]-2-cloro-etanona

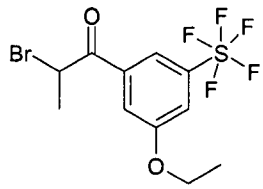


Se disolvió 1-{3-terc-butil-5-[2-(tetrahidro-piran-2-iloxi)-etoximetil]-fenil}-etanona (O2.063; 2,0 g) en metanol/THF (30 ml/30 ml) y se mezcló, al tiempo con tribromuro de feniltrimetilamonio (2,25 g) mientras se agitaba. Después de agitar a TA durante 3 h, la mezcla se diluyó con DCM y se lavó una vez con una solución al 5% de tiosulfato sódico, y la fase de DCM se secó sobre sulfato de magnesio y se concentró mediante evaporación rotatoria. El residuo se disolvió en THF (200 ml) y se añadió HCl 3 N (30 ml). Después de reposar durante 1 h, se añadieron EA y agua y se separó la fase de EA. La fase de EA se secó sobre sulfato de magnesio y se concentró mediante evaporación rotatoria. El residuo se purificó usando gel de sílice (cartucho de 40 g, gradiente de 0-50% de n-heptano/EA en 40 min). Se obtuvieron 774 mg del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,87 (1 H), 7,76 (1 H), 7,67 (1 H), 5,21 (2 H), 4,66 (1 H), 4,56 (2 H), 3,56 (2 H), 3,49 (2 H), 1,32 (9 H)

O1.064

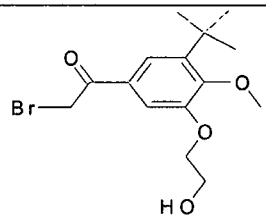
2-Bromo-1-[3-etoxi-5-(pentafluorosulfanil)-fenil]-propan-1-ona



1-[3-Etoxi-5-(pentafluorosulfanil)fenil]propan-1-ona (O2.064; 150 mg) se disolvió en THF (15 ml) y se añadió tribromuro de feniltrimetilamonio (185 mg) mientras se agitaba a TA. Después de agitar a TA durante 5 h, la mezcla se combinó con agua y solución saturada de hidrógeno-carbonato de sodio y se añadió EA. La fase en EA se separó y la fase en agua alcalina se extrajo tres veces con EA. Las fases orgánicas reunidas se lavaron una vez con solución saturada de cloruro de sodio, se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El producto bruto se purificó mediante HPLC preparativa HPLC (met. A). Las fracciones de producto, cada una de ellas pura, se combinaron, se liberaron del acetonitrilo a presión reducida, se alcalinizaron con solución saturada de hidrógeno-carbonato de sodio y se extrajeron cinco veces con EA. Las fases orgánicas combinadas se

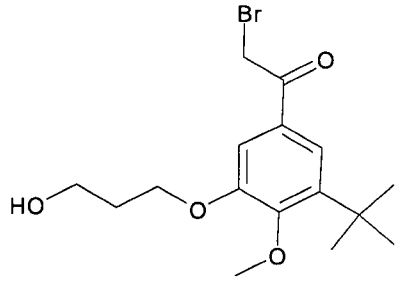
secaron sobre sulfato de magnesio y, después de separar por filtración el desecante, se secaron a presión reducida. Se aislaron 120 mg del compuesto del título.

Tr de LC-MS: 1,29 min [M+H$^+$]: 383,0 (met. b)

Número		Tr de LC-MS	[M+H$^+$]:	Comentario:
O1.070		0,96 min	345,1 (met. b)	Preparación análoga a O1.071: O2.070; 6,66 g, producto: 3,3 g

O1.071

2-Bromo-1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]etanona

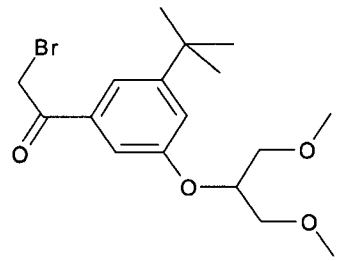


Se disolvió 1-{3-terc-butil-4-metoxi-5-[3-(tetrahidropiran-2-iloxi)propoxi]fenil}etanona (O2.071; 12,7 g) en metanol/THF (200/200 ml) y se mezcló con tribromuro de feniltrimetilamonio (13,1 g) mientras se agitaba. La mezcla se agitó a TA durante 1 h, después se diluyó con DCM y se lavó una vez con una solución al 5% de tiosulfato sódico. La fase de DCM se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se recogió en acetonitrilo (100 ml) y se mezcló con ácido clorhídrico al 48% (5.91 ml). La mezcla se dejó en reposo durante 1 h, después se mezcló con agua, se extrajo por agitación con EA y las fases de EA combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó usando gel de sílice (cartucho de 120 g, gradiente de 0-100% de n-heptano/MtB éter en 60 min). Se obtuvieron 3,29 g del compuesto del título.

Tr de LC-MS: 1,01 min [M+H$^+$]: 359,1 (met. b)

O1.072

2-Bromo-1-[3-terc-butil-5-(2-metoxi-1-metoximetil-etoxi)-fenil]-etanona

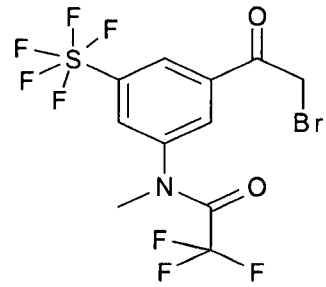


1-[3-terc-Butil-5-(2-metoxi-1-metoximetiletoxi)fenil]etanona (O2.072; 1,64 g) se disolvió en metanol/THF (30/30 ml) y se mezcló, al tiempo que se agitaba, con tribromuro de feniltrimetilamonio (2,09 g). La mezcla se agitó a TA durante 1 h, luego se diluyó con DCM y se lavó una vez con solución de tiosulfato de sodio al 5%. La fase en DCM se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 80 g, gradiente de 0-30% de n-heptano/MtB-éter en 60 min). Se obtuvieron 890 mg del compuesto del título.

Tr de LC-MS: 1,77 min [M+H$^+$]: 373,0 (met. a)

O1.075

N-[3-(2-Bromoacetil)-5-(pentafluorosulfanil)fenil]-2,2,2-trifluoro-N-metilacetamida

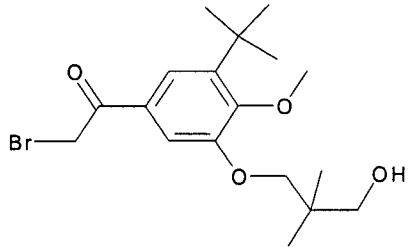


Se disolvió N-[3-acetil-5-(pentafluorosulfanil)fenil]-2,2,2-trifluoro-N-metilacetamida (O2.075; 1,03 g) en una mezcla de metanol (20 ml) y THF (20 ml). Se añadió tribromuro de feniltrimetilamonio (1,05 g) mientras se agitaba. Después de agitar a TA durante 5 h, la mezcla se dejó en reposo durante una noche, después se añadió más cantidad de tribromuro de feniltrimetilamonio (100 mg) y la mezcla se calentó a 60°C durante 2 h. Después de un periodo de refrigeración, la mezcla de reacción se añadió a ácido sulfúrico 2 N y se agitó durante 10 min. Después, la fase acuosa se extrajo tres veces con EA. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y, después de que el desecante se retirara por filtración, se secaron a presión reducida. Se obtuvieron 1,2 g del compuesto del título, que tenía suficiente pureza para las siguientes reacciones.

Tr de LC-MS: 1,72 min [M+H$^+$]: 449,9 (met. a)

O1.085

2-Bromo-1-[3-terc-butil-5-(3-hidroxi-2,2-dimetil-propoxi)-4-metoxi-fenil]-etanona

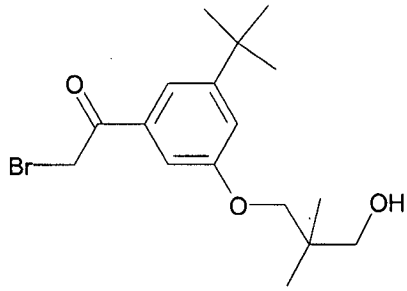


3-(5-acetil-3-terc-butil-2-metoxi-fenoxi)-2,2-dimetil-propil éster del ácido acético (O2.085; 1,16 g) se convirtió y se trató de forma análoga a O1.008. La purificación utilizando gel de sílice se realizó como se indica a continuación: (cartucho de 80 g, gradiente de 0-70% de n-heptano/MtB-éter en 60 min). Se obtuvieron 867 mg del compuesto del título.

Tr de LC-MS: 1,80 min [M+H$^+$]: 387,1 (met. a)

O1.086

2-Bromo-1-[3-terc-butil-5-(3-hidroxi-2,2-dimetil-propoxi)-fenil]-etanona

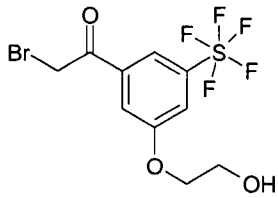


1-[3-terc-Butil-5-(3-hidroxi-2,2-dimetilpropoxi)fenil]etanona (O2.086; 388 mg) se convirtió, se trató y se purificó de forma análoga a O1.085. Se obtuvieron 311 mg del compuesto del título.

Tr de LC-MS: 1,78 min [M+H$^+$]: 357,0 (met. a)

O1.090

2-Bromo-1-[3-(2-hidroxi-etoxi)-5-(pentafluorsulfanil)-fenil]-etanona



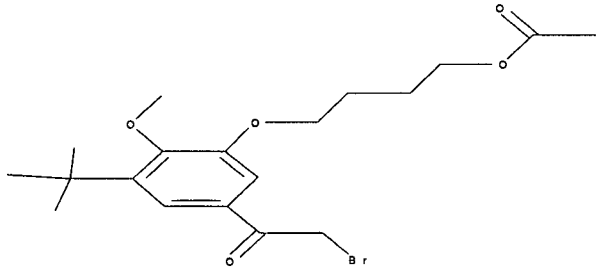
1-{3-(Pentafluorosulfanil)-5-[2-(tetrahidropiran-2-iloxi)etoxi]fenil}etanona (O2.090;

813 mg) se convirtió, se trató y se purificó de forma análoga a O1.071. Sin embargo, el tiempo de reacción fue de tres horas en lugar de una. Se obtuvieron 174 mg del compuesto del título.

Tr de LC-MS: 0,94 min [M+H$^+$]: 385,0 (met. b)

O1.095

4-[5-(2-Bromo-acetil)-3-terc-butil-2-metoxi-fenoxi]-butil éster del ácido acético

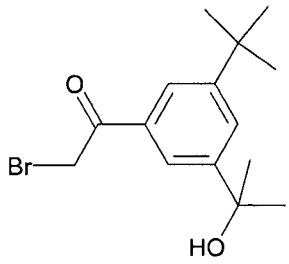


Acetato de 4-(5-acetil-3-terc-butil-2-metoxifenoxi)butilo (O2.095; 10,51 g) se convirtió, se trató y se purificó de forma análoga a O1.071. Se obtuvieron 4,81 g del compuesto del título.

Tr de LC-MS: 1,21 min [M+H$^+$]: 415,1 (met. b)

O1.100

2-Bromo-1-[3-terc-butil-5-(1-hidroxi-1-metil-etil)-fenil]-etanona

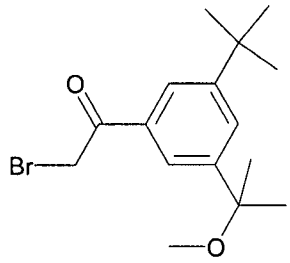


1-[3-terc-Butil-5-(1-hidroxi-1-metiletil)fenil]etanona (O2.100; 50 mg) se cargo inicialmente en THF (5 ml) mientras se agitaba a TA, y se mezcló con tribromuro de feniltrimetilamonio (80 mg). Después de agitar a TA durante 3 h, la mezcla se dejó reposar durante una noche y se mezcló con agua y solución saturada de hidrógeno-carbonato de sodio. Luego se extrajo tres veces con EA, y las fases en EA combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó utilizando gel de sílice (cartiucho de 10 g, gradiente de n-heptano/EA). Se obtuvieron 42 mg del compuesto del título.

Tr de LC-MS: 1,10 min [M+H$^+$-OH]: 295,1 (met. b)

O1.101

2-Bromo-1-[3-terc-butil-5-(1-metoxi-1-metil-etil)-fenil]-etanona

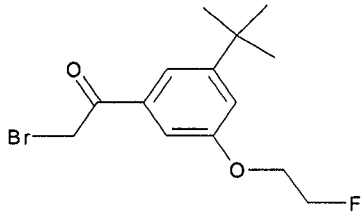


1-[3-terc-butil-5-(1-hidroxi-1-metiletil)fenil]etanona (O2.100; 500 mg) se cargó inicialmente en una mezcla de THF y metanol (3,5/3,5 ml) mientras se agitaba a TA, y se mezcló con tribromuro de feniltrimetilamonio (800 mg). Después de agitar a TA durante 7 h, la emzcla se combinó con agua y solución saturada de hidrógeno-carbonato de sodio. Luego se extrajo tres veces con EA, y las fases en EA combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó utilizando gel de sílice (cartucho de 70 g, gradiente de n-heptano/EA). Se obtuvieron 454 mg del compuesto del título.

Tr de LC-MS: 1,23 min [M+H$^+$-OH]: 295,1 (met. b)

O1.105

2-Bromo-1-[3-terc-butil-5-(2-fluor-etoxi)-fenil]-etanona

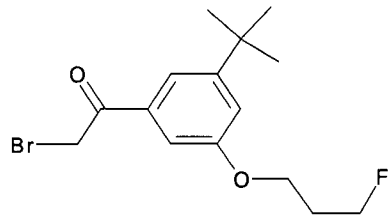


Se disolvió 1-[3-terc-butil-5-(2-fluoro-etoxi)-fenil]-etanona (O2.105; 600 mg) en metanol/THF (15/15 ml). Se añadió tribromuro de feniltrimetilamonio (950 mg) mientras se agitaba. Después de agitar a TA durante 3 h, se añadió agua (5 ml) y la mezcla se secó. El residuo se mezcló con DCM (200 ml) y una solución saturada de hidrógeno-carbonato sódico (100 ml). La fase de DCM se separó y la fase acuosa se extrajo tres veces más con DCM. Las fases en DCM combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron. El residuo se purificó usando gel de sílice (cartucho de 50 g, gradiente de 0-60% de n-heptano/EA en 40 min). Se obtuvieron 560 mg del compuesto del título.

Tr de LC-MS: 1,19 min [M+H$^+$]: 317,1 (met. b)

O1.106

2-Bromo-1-[3-terc-butil-5-(3-fluoropropoxi)-fenil]-etanona

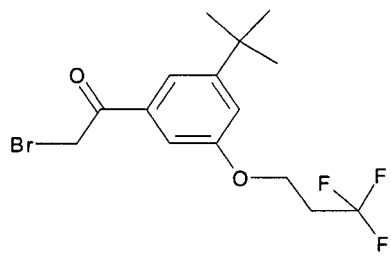


1-[3-terc-Butil-5-(3-fluoropropoxi)fenil]etanona (630 mg) se convirtió, se trató y se purificó de forma análoga a O1.105. Se obtuvieron 510 mg del compuesto del título.

Tr de LC-MS: 1,23 min [M+H$^+$]: 331,1 (met. b)

O1.107

2-Bromo-1-[3-terc-butil-5-(3,3,3-trifluoro-propoxi)-fenil]-etanona

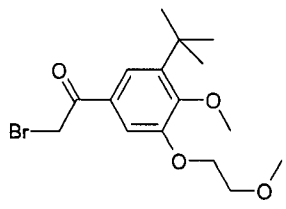


1-[3-terc-Butil-5-(3,3,3-trifluoropropoxi)fenil]etanona (O2.107; 170 mg, 0,59 mmol) se disolvió en una mezcla de THF (3 ml) y metanol (3 ml). Mientras se agitaba se introdujo tribromuro de feniltrimetilamonio (222 mg, 0,59 mmol) y la mezcla se agitó durante una noche. La mezcla de reacción se diluyó con acetato de etilo y se lavó con solución saturada de hidrógeno-carbonato de sodio. Después de secar sobre sulfato de sodio, el disolvente se separó y el residuo se purificó mediante cromatografía de resolución rápida (n-heptano:acetato de etilo). Rendimiento: 42 mg,

Tr de LC-MS: 1,19 min [M+H$^+$]: 367,1 (met. b)

O1.110

2-Bromo-1-[3-terc-butil-4-metoxi-5-(2-metoxi-etoxi)-fenil]-etanona

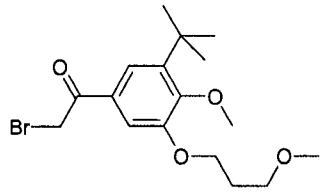


1-[3-terc-Butil-4-metoxi-5-(2-metoxietoxi)fenil]etanona (O2.110; 1,17 g) se convirtió, se trató y se purificó de forma análoga a O1.008. Se obtuvieron 1,18 g del compuesto del título.

Tr de LC-MS: 1,10 min [M+H$^+$]: 359,1 (met. b)

O1.111

2-Bromo-1-[3-terc-butil-4-metoxi-5-(3-metoxi-propoxi)-fenil]-etanona



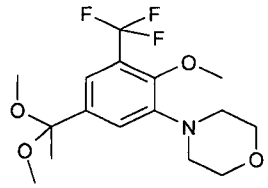
1-[3-terc-Butil-4-metoxi-5-(3-metoxipropoxi)fenil]etanona (O2.111; 1,49 g) se convirtió, se trató y se purificó de forma análoga a O1.008. Se obtuvieron 1,65 g del compuesto del título.

Tr de LC-MS: 1,16 min [M+H$^+$]: 373,0 (met. b)

O2

O2.004

4-[5-(1,1-Dimetoxi-etil)-2-metoxi-3-trifluorometil-fenil]-morfolina

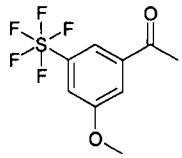


1-Bromo-5-(1,1-dimetoxietil)-2-metoxi-3-trifluorometilbenceno (O3.004; 700 mg) se cargó inicialmente en dioxano (7 ml) y se mezcló sucesivamente con acetato de Pd(II) (46 mg), carbonato de cesio (2 g), 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (118 mg) y morfolina (0,27 ml). Después de ello, la mezcla de reacción se calentó hasta 90°C durante 7 h y luego se dejó reposar durante una noche. Subsiguientemente, se filtró y el filtrado se concentró mediante evaporación rotatoria. El residuo se purificó utilizando gel de sílice (cartucho de 50 g, gradiente de n-heptano/EA). Se obtuvieron 433 mg del compuesto del título.

Tr de LCMS: 1,55 min [M+H$^+$]: 304,0 (met. a)

O2.007

1-[3-Metoxi-5-(pentafluorosulfanil)-fenil]-etanona

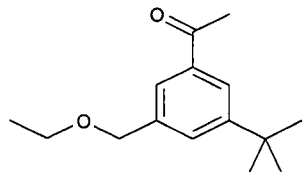


Se disolvió 3,N-dimetoxi-N-metil-5-(pentafluorosulfanil)-benzamida (O3.007; 2,0 g) en THF absoluto (60 ml) y mientras se agitaba a 0°Cse añadió gota a gota bromuro de metilmagnesio (5,2 ml, 3 M en éter dietílico). Después de la adición, el baño de hielo se retiró y la mezcla se agitó durante 2 h a TA. Mientras se enfriaba, se añadió luego ácido clorhídrico 1 N, seguido de agua y acetato de etilo. La fase orgánica se separó y la fase acuosa se extrajo dos veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó mediante HPLC preparativa (met. A). Las fracciones que contenían producto se combinaron, se liberaron del acetonitrilo a presión reducida y se extrajeron tres veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. Se obtuvieron 1,63 g del compuesto deseado.

^{1}H RMN (400 MHz, DMSO-d6) [ppm]: 7,87 (1 H), 7,75 (1 H), 7,67 (1 H), 3,91 (3 H), 2,64 (3 H)

O2.008

1-(3-terc-Butil-5-etoximetil-fenil)-etanona

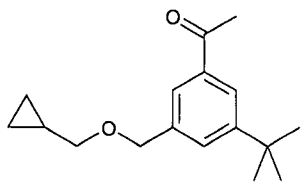


Se hizo reaccionar 3-terc-butil-N-metoxi-5-metoximetil-N-metil-benzamida (O3.008; 854 mg) de forma análoga a O2.043. Se obtuvieron 550 mg del compuesto del título.

Tr de LCMS: 1,70 min [M+H$^+$]: 235,3 (met. a)

O2.009

1-(3-terc-Butil-5-ciclopropilmetoximetil-fenil)-etanona

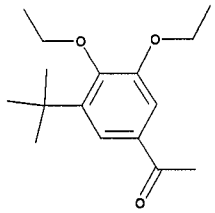


Partiendo de 3-terc-butil-5-hidroximetilbenzoato de metilo y bromuro de ciclopropilmetilo, el compuesto del título (600 mg) se preparó de forma análoga a O5.008 hasta O2.008.

Tr de LCMS: 1,81 min [M+H$^+$]: 261,2 (met. a)

O2.010

1-(3-terc-Butil-4,5-dietoxi-fenil)-etanona

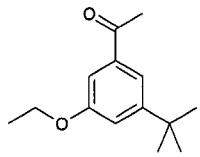


Se disolvieron 1-(3-terc-butil-4-etoxi-5-hidroxi-fenil)-etanona (O3.010; 470 mg) y yoduro de etilo (193 µl) en DMF (6,2 ml) y se añadió hidruro sódico (57 mg). Después de agitar durante 0,5 h a TA, la DMF se retiró y el residuo se recogió en EA, se lavó con agua, se secó y se concentró. El residuo se purificó sobre gel de sílice (cartucho de 40 g, gradiente de 0-30% de n-heptano/EA en 60 min). Se obtuvieron 420 mg del compuesto del título.

Tr de LCMS: 1,93 min [M+H$^+$]: 265,2 (met. a)

O2.011

1-(3-terc-Butil-5-etoxi-fenil)-etanona

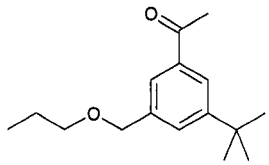


3-terc-butil-5-hidroxibenzoato de metilo (O6.043) se hizo reaccionar con yoduro de etilo de forma análoga a O5.043 y se convirtió en el compuesto del título de forma análoga a la secuencia O4.043 a O2.043. Se obtuvieron 390 mg.

Tr de LCMS: 1,72 min [M+H$^+$]: 221,3 (met. a)

O2.012

1-(3-terc-Butil-5-propoximetil-fenil)-etanona

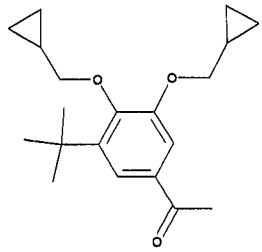


Partiendo de 3-terc-butil-5-hidroximetil-benzoato de metilo y yoduro de propilo, el compuesto del título (333 mg) se preparó de forma análoga a O5.008 a O2.008.

Tr de LCMS: 1,81 min [M+H$^+$]: 261,2 (met. a)

O2.013

1-(3-terc-Butil-4,5-bis-ciclopropilmetoxi-fenil)-etanona

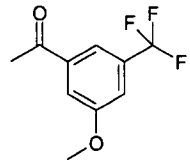


Partiendo de 2-bromo-6-terc-butil-4-(1,1-dimetoxi-etil)-fenol y bromuro de ciclopropilo, el compuesto del título (547 mg) se preparó de forma análoga a O4.010 a O2.010.

Tr de LCMS: 2,10 min [M+H$^+$]: 317,4 (met. a)

O2.014

1-(3-Metoxi-5-trifluorometil-fenil)-etanona

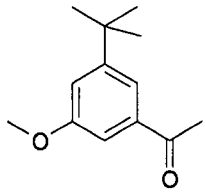


3,N-Dimetoxi-N-metil-5-trifluorometilbenzamida (O3.014, 460 mg) se cargo inicialmente en THF (15 ml) a TA disuelto en Ar. Después de ello, la mezcla se enfrió hasta 0°C y se añadió gota a gota bromuro de metilmagnesio (1,5 ml; 3 M en dietil-éter). Subsiguientemente, se retiró el baño de hielo y la mezcla se agitó a TA durante 2 h. Luego, la mezcla se combinó con ácido clorhídrico 1 N mientras se enfriaba con hielo, se diluyó con agua y se extrajo tres veces con EA. Las fases en EA combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. Se aislaron 349 mg del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,80 (1 H), 7,73 (1 H), 7,53 (1 H), 3,92 (3 H), 2,66 (3 H)

O2.015

1-(3-terc-Butil-5-metoxi-fenil)-etanona

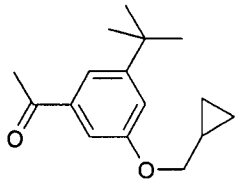


Se hizo reaccionar 3-terc-butil-5-hidroxibenzoato de metilo (O6.043) con yoduro de metilo de forma análoga a O5.043 y el compuesto del título se convirtió de forma análoga a la secuencia O4.043 a O2.043. Se obtuvieron 880 mg.

Tr de LCMS: 1,65 min [M+H$^+$]: 207,1 (met. a)

O2.016

1-(3-terc-Butil-5-ciclopropilmetoxi-fenil)-etanona

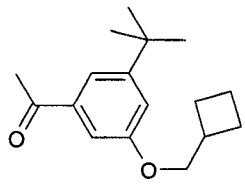


3-terc-Butil-5-hidroxibenzoato de metilo (O6.043) se hizo reaccionar con bromuro de ciclopropilmetilo de forma análoga a O5.043, y se convirtió en el compuesto del título de forma análoga a la secuencia O4.043 a O2.043. Se obtuvieron 1,02 g.

Tr de LCMS: 1,86 min [M+H$^+$]: 247,1 (met. a)

O2.017

1-(3-terc-Butil-5-ciclobutilmetoxi-fenil)-etanona

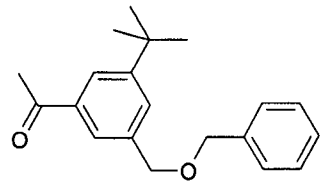


3-terc-Butil-5-hidroxibenzoato de metilo (O6.043) se hizo reaccionar con bromometilciclobutano de forma análoga a O5.043, y se convirtió en el compuesto del título de forma análoga a la secuencia O4.043 a O2.043. Se obtuvieron 252 mg.

Tr de LCMS: 2,07 min [M+H$^+$]: 261,2 (met. a)

O2.018

1-(3-Benciloximetil-5-terc-butil-fenil)-etanona

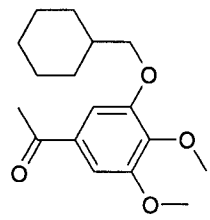


3-terc-Butil-5-hidroximetilbenzoato de metilo se hizo reaccionar con bromuro de bencilo de forma análoga a O5.043, y se convirtió en el compuesto del título de forma análoga a la secuencia O4.008 a O2.008. Se obtuvieron 638 mg.

Tr de LCMS: 1,93 min [M+H$^+$]: 297,2 (met. a)

O2.019

1-(3-Ciclohexilmetoxi-4,5-dimetoxi-fenil)-etanona

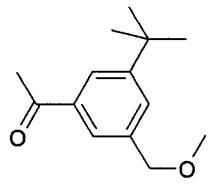


3-Ciclohexilmetoxi-4,5,N-trimetoxi-N-metilbenzamida (420 mg) se convirtió y se trató de forma análoga a O2.059. No se realizó purificación en gel de sílice alguna. Se obtuvieron 370 mg.

Tr de LCMS: 1,82 min [M+H$^+$]: 293,2 (met. a)

O2.020

1-(3-terc-Butil-5-metoximetil-fenil)-etanona

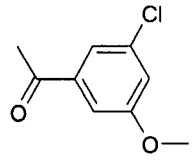


3-terc-Butil-5-hidroximetilbenzoato de metilo se hizo reaccionar con yoduro de metilo de forma análoga a O5.043, y se convirtió en el compuesto del título de forma análoga a la secuencia O4.008 a O2.008. Se obtuvieron 1,54 g.

Tr de LCMS: 1,58 min [M+H$^+$]: 221,1 (met. a)

O2.021

1-(3-Cloro-5-metoxi-fenil)-etanona

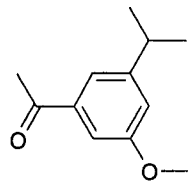


Ácido 3-cloro-5-metoxibenzoico (3 g) se hizo reaccionar de forma análoga a O3.043/O2.043 con cloruro de tionilo (23,3 ml) e hidrocloruro de N,O-dimetilhidroxilamina (1,57 g) y bromuro de metilmagnesio (8,91 ml). Se obtuvieron 2,42 g.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,54 (1 H), 7,40 (1 H), 7,30 (1 H), 3,84 (3 H), 2,58 (3 H)

O2.030

1-(3-Isopropil-5-metoxi-fenil)-etanona

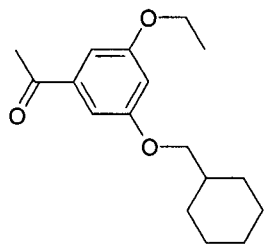


3-hidrixo-5-isopropilbenzoato de metilo se hizo reaccionar con yoduro de metilo de forma análoga a O5.043, y se convirtió en el compuesto del título de forma análoga a la secuencia O4.043 a O2.043. Se obtuvieron 425 mg.

Tr de LC-MS: 1,54 min [M+H$^+$]: 193,1 (met. a)

O2.031

1-(3-Ciclohexilmetoxi-5-etoxi-fenil)-etanona



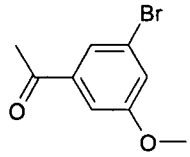
1-(3,5-Dihidroxifenil)etanona (1,0 g) y bromuro de etilo (0,531 ml) se disolvieron a TA en DMF (20 ml) y se añadió hidruro de sodio (189 mg). Después de agitar a 50°C durante 2 h, se añadió bromuro de ciclohexilmetilo (1,36 ml), seguido de hidruro de sodio adicional (315 mg). Después de agitar a 50°C durante otras 2 h, la DMF se retiró y el residuo se recogió en EA, se lavó con agua, se secó, se filtró y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 80 g, gradiente

de 0-20% de n-heptano/EA en 60 min). Se obtuvieron 378 mg del compuesto del título.

Tr de LC-MS: 2,07 min [M+H$^+$]: 277,2 (met. a)

O2.032

1-(3-Bromo-5-metoxi-fenil)-etanona

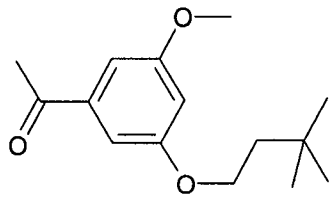


3-Bromo-5-metoxibenzoato de metilo (O5.032; 2,50 g) se convirtió en el compuesto del título de forma análoga a las secuencias O4.043, O3.043 y O2.059. Se obtuvieron 1,45 g.

Tr de LC-MS: 1,46 min [M+H$^+$]: 229,0 (met. a)

O2.033

1-[3-(3,3-Dimetilbutoxi)-5-metoxifenil]etanona

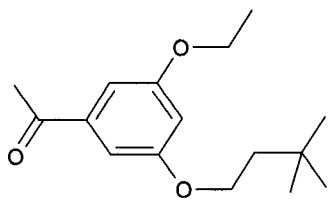


1-(3-Hidroxi-5-metoxifenil)etanona (O3.033; 1,12 g) y 1-yodo-3,3-dimetilbutano (1,57 g) se disolvieron en DMF, y se añadió hidruro de sodio (194 mg). Después de agitar a TA durante 2 h, la DMF se separó. El residuo se recogió en EA, se lavó con agua, se secó, se filtró y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 40 g, 0-50% de n-heptano/EA en 30 min). Se obtuvieron 850 mg del compuesto del título.

Tr de LC-MS: 1,83 min [M+H$^+$]: 251,1 (met. a)

O2.034

1-[3-(3,3-Dimetilbutoxi-5-etoxifenil]etanona

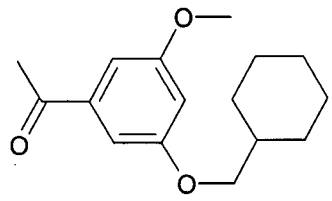


1-(3,5-Dihidroxifenil)etanona (3,0 g) se convirtió de forma análoga a O2.031. Isin embargo, en lugar de bromuro de ciclohexilo se utilizó 1-bromo-3,3-dimetilbutano. Después de cromatohgrafía, se obtuvieron 960 mg del compuesto del título.

Tr de LC-MS: 1,99 min [M+H$^+$]: 265,2 (met. a)

O2.035

1-(3-Ciclohexilmetoxi-5-metoxifenil)etanona

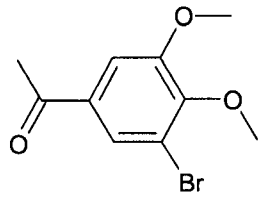


1-(3-Hidroxi-5-metoxifenil)etanona (O3.033; 1,5 g) y bromometilciclohexano (1,76 g) se disolvieron en DMF (20 ml) y se añadió hidruro de sodio (260 mg). Después de agitar a 50°C durante 24 h, la DMF se separó. El residuo se recogió en EA, se lavó con agua, se secó, se filtró y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 40 g, 0-50% de n-heptano/EA en 30 min). Se obtuvieron 1,33 g del compuesto del título.

Tr de LC-MS: 1,93 min [M+H$^+$]: 263,2 (met. a)

O2.040

1-(3-Bromo-4,5-dimetoxifenil)etanona

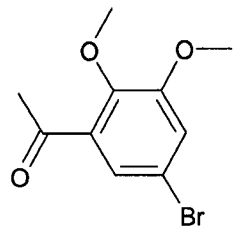


Ácido 3-bromo-4,5-dimetoxibenzoico (2,0 g) se convirtió en el derivado de benzamida de forma análoga a O3.043, y esta última se convirtió en el compuesto del título de forma análoga a O2.059. Se obtuvieron 1,22 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,78 (1 H); 7,53 (1 H); 3,90 (3 H); 3,82 (3 H); 2,57 (3 H)

O2.041

1-(5-Bromo-2,3-dimetoxifenil)etanona

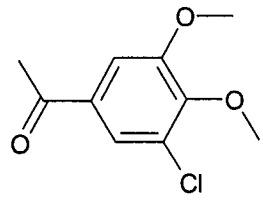


Ácido 5-bromo-2,3-dimetoxibenzoico (2 g) se convirtió en el derivado de benzamida de forma análoga a O3.043, y esta última se convirtió en el compuesto del título de forma análoga a O2.059. Se obtuvieron 1,1 g del compuesto del título.

Tr de LC-MS: 3,70 min [M+H$^+$]: 259,0 (met. d)

O2.042

1-(3-Cloro-4,5-dimetoxifenil)etanona

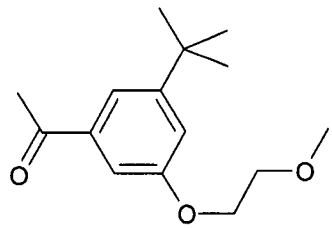


Ácido 3-cloro-4,5-dimetoxibenzoico (1 g) se convirtió en el derivado de benzamida de forma análoga a O3.043, y este último en el compuesto del título de forma análoga a O2.059. Se obtuvieron 495 mg del compuesto del título.

Tr de LC-MS: 1,55 min [M+H$^+$]: 215,1 (met. a)

O2.043

1-[3-terc-Butil-5-(2-metoxietoxi)fenil]etanona



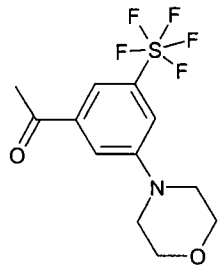
Se disolvió 3-terc-butil-N-metoxi-5-(2-metoxietoxi)-N-metilbenzamida (O3.043; 1,35 g) en THF (40 ml), se añadió gota a gota bromuro de metilmagnesio (3,05 ml, 3 M en éter) a 0°Cy después la mezcla se agitó a TA durante 2 h. Después, la mezcla se combinó con ácido clorhídrico 1 N (50 ml), se diluyó con agua y se extrajo con agitación tres veces con EA. Después, las capas de EA combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó usando gel de sílice (cartucho de 40 g, gradiente de 0-30% de n-heptano/EA en 30

min). Se obtuvieron 1,0 g del compuesto del título.

Tr de LC-MS: 1,58 min [M+H$^+$]: 251,3 (met. a)

O2.044

1-[3-Morfolin-4-il-5-(pentafluorosulfanil)-fenil]-etanona

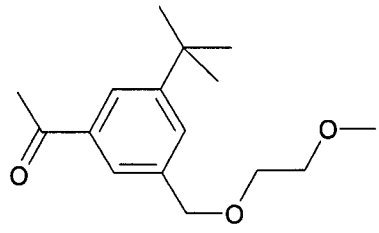


N-Metoxi-N-metil-3-morfolin-4-il-5-(pentafluorosulfanil)benzamida (O3.044; 2,38 g) se convirtió y se trató de forma análoga a O2.043. La purificación se efectuó utilizando gel de sílice (cartucho de 80 g, gradiente de 0-70% de n-heptano/EAen 40 min). Se obtuvieron 1,1 g del compuesto del título.

Tr de LC-MS: 1,57 min [M+H$^+$]: 332,0 (met. a)

O2.045

1-[3-terc-Butil-5-(2-metoxietoximetil)fenil]etanona

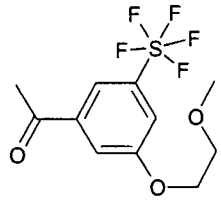


3-terc-Butil-5-hidroximetilbenzoato de metilo (6,0 g) se hizo reaccionar de forma análoga a O5.043 con 1-bromo-2-metoxietano para dar 3-terc-butil-5-(2-metoxietoximetil)benzoato de metilo. Este ultimo se convirtió luego en el compuesto del título de forma análoga a la secuencia de O4.043 a O2.043. Se obtuvieron 508 mg del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,35 (1 H); 7,73 (1 H), 7,63 (1 H); 4,56 (2 H); 3,58 (2 H); 3,50 (2 H); 3,26 (3 H); 2,58 (3 H); 1,32 (9 H)

O2.050

1-[3-(2-Metoxi-etoxi)-5-(pentafluorosulfanil)-fenil]-etanona

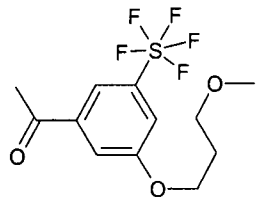


1-[3-Hidroxi-5-(pentafluorosulfanil)fenil]etanona (O3.050; 592 mg) y 1-bromo-2-metoxietano (255 µl) se disolvieron en DMF (14,8 ml), y se añadió hidruro de sodio (65 mg). Después de agitar a TA durante 2 h, se añadió bromuro adicional (80 µl) y la mezcla se calentó hasta 50°C durante 12 h. Después se separó la DMF y el residuo se recogió en EA, se lavó con agua, se secó, se filtró y se concentró. Se obtuvieron 578 mg del compuesto del título.

Tr de LC-MS: 1,58 min [M+H$^+$]: 321,1 (met. a)

O2.051

1-[3-(2-Metoxi-etoxi)-5-(pentafluorosulfanil)-fenil]-etanona

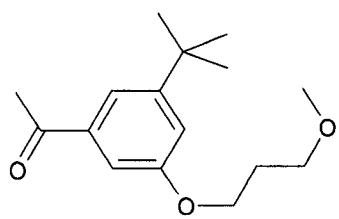


1-[3-Hidroxi-5-(pentafluorosulfanil)fenil]etanona (O3.050; 700 mg) y 1-bromo-2-metoxipropano (490 mg) se disolvieron en DMF (10 ml) y se añadió hidruro de sodio (77 mg). Después de agitar a TA durante 2 h, se añadió bromuro adicional (100 µl) y la mezcla se calentó hasta 50°C durante 6 h. Después se separó la DMF y el residuo se recogió en EA, se lavó con agua, se secó, se filtró y se concentró. Se obtuvieron 670 mg del compuesto del título.

Tr de LC-MS: 1,71 min [M+H$^+$]: 335,1 (met. a)

O2.052

1-[3-terc-Butil-5-(3-metoxi-propoxi)-fenil]-etanona



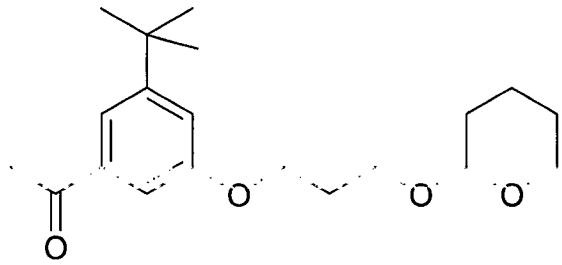
Partiendo de 3-terc-butil-5-hidroxibenzoato de metilo (O6.043) y 1-bromo-3-metoxi-

propano, se siguió la secuencia de síntesis O5.043 a O2.043. Se obtuvieron 880 mg del compuesto del título.

Tr de LC-MS: 1,71 min [M+H$^+$]: 265,3 (met. a)

O2.059

1-[3-terc-butil-5-(3-hidroxi-propoxi)-fenil]-etanona

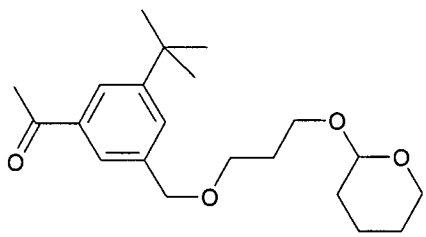


Se disolvió 3-terc-butil-N-metoxi-N-metil-5-[3-(tetrahidro-piran-2-iloxi)-propoxi]-benzamida (O3.059; 5,49 g) en THF (100 ml), se enfrió a 0°C y se mezcló con litio-bis-(trimetilsilil)-amida (14,47 ml, 1M en MtB-éter). Después de agitar durante 30 min a 0°C, se añadió gota a gota bromuro de metilmagnesio (9,65 ml, 3 M en éter). El baño de refrigeración se retiró y, después de agitar durante 2 h a TA, la mezcla se diluyó con agua y se extrajo sacudiendo con EA. La fase de EA se secó sobre sulfato de magnesio, se filtró y se concentró por evaporación rotatoria. El residuo se purificó usando gel de sílice (200 g, 4:1 de n-heptano/EA). Se obtuvieron 3,4 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,53 (1 H), 7,23 (1 H), 7,17 (1 H), 4,57 (1 H, -O-C(-C)H-O-), 4,11 (2 H), 2,57 (3 H)

O2.060

1-{3-terc-Butil-5-[3-(tetrahidropiran-2-iloxi)propoximetil]fenil}etanona



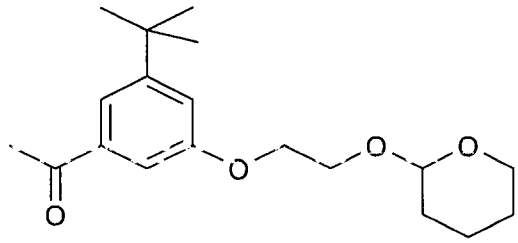
3-terc-Butil-5-hidroximetilbenzoato de metilo (3,5 g) se hizo reaccionar con 2-(3-bromopropoxi)tetrahidropirano de forma análoga a O5.063 para dar 3-terc-butil-5-[3-(tetrahidropiran-2-iloxi)propoximetil]benzoato de metilo, y este último se convirtió subsiguientemente en el compuesto del título de acuerdo con la secuencia O4.059

a O2.059. Se obtuvieron 1,75 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,84 (1 H); 7,73 (1 H); 7,61 (1 H); 4,53 (2 H); 4,51 (1 H, -O-C(-C)H-O-), 2,58 (3 H)

O2.061

1-{3-terc-Butil-5-[2-(tetrahidro-piran-2-iloxi)-etoxi]-fenil}-etanona

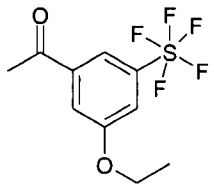


Partiendo de 3-terc-butil-5-hidroxibenzoato de metilo (O6.043) y 2-(2-bromoetoxi)-tetrahidropirano, se siguió la secuencia de síntesis O5.059 a O2.059. Se obtuvieron 3,9 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,53 (1 H), 7,31 (1 H), 7,20 (1 H), 4,66 (1 H, -O-C(-C)H-O-), 4,20 (2 H), 2,58 (3 H)

O2.062

1-[3-Etoxi-5-(pentafluorosulfanil)-fenil]-etanona

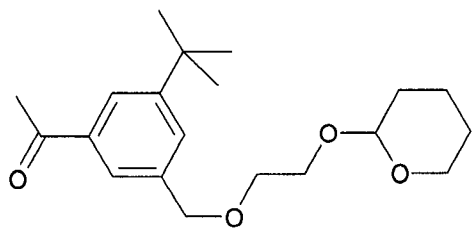


3-Etoxi-N-metoxi-N-metil-5-(pentafluorosulfanil)benzamida (O3.062; 2,60 g) se convirtió y se trató de forma análoga a O2.007. No se llevó a cabo purificación utilizando gel de sílice. Se obtuvieron 2,25 g del compuesto del título.

Tr de LC-MS: 1,72 min [M+H$^+$]: 291,0 (met. a)

O2.063

1-{3-terc-Butil-5-[2-(tetrahidropiran-2-iloxi)etoximetil]fenil}etanona

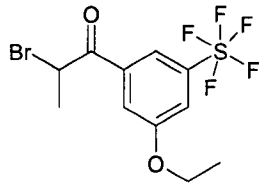


3-terc-Butil-5-[2-(tetrahidropiran-2-iloxi)etoximetil]benzoato de metilo (O5.063, 2,28 g) se convirtió en el compuesto del título de forma análoga a la secuencia O4.059 a O2.059. Se obtuvieron 2,0 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,85 (1 H); 7,74 (1 H); 7,63 (1 H); 4,60 (1 H, -O-C(-C)H-O-), 4,58 (2 H), 2,58 (3 H)

O2.064

1-[3-Etoxi-5-(pentafluorosulfanil)-fenil]-propan-1-ona

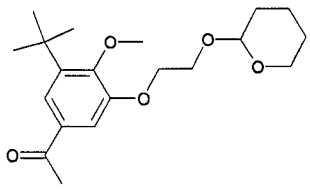


3-Etoxi-N-metoxi-N-metil-5-(pentafluorosulfanil)benzamida (O3.062; 170 mg) se disolvió en THF absoluto (5 ml), y se añadió, gota a gota y mientras se agitaba, bromuro de etilmagnesio (0,65 ml; 2 M en dietiléter) a 0°C. Después de la adición se retiró el baño de hielo y la mezcla se agitó a TA durante 2 h. Luego se añadió bromuro de etilmagnesio adicional (0,1 ml) y la mezcla se agitó una vez más durante 2 h. Al tiempo que se enfriaba se añadió subsiguientemente, gota a gota, ácido clorhídrico 1 N, seguido de agua y acetato de etilo. La fase orgánica se separó y la fase acuosa se extrajo dos veces más con acetato de etilo. Los extractos reunidos se secaron sobre sulfato de magnesio, se filtraron y se concentraron. Se obtuvieron 150 mg del compuesto deseado.

Tr de LC-MS: 1,26 min [M+H$^+$]: 305,1 (met. b)

O2.070

1-{3-terc-Butil-4-metoxi-5-[2-(tetrahidro-piran-2-iloxi)-etoxi]-fenil}-etanona



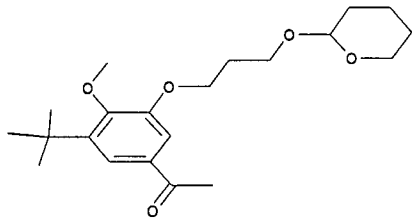
De forma análoga a O2.071, 1-(3-terc-butil-5-hidroxi-4-metoxifenil)etanona (O3.070; 5,0 g) se hizo reaccionar con 2-(2-bromoetoxi)tetrahidropirano (5,64 g). Sin embargo, el producto bruto se purificó utilizando gel de sílice (cartucho de 40 g, gradiente de 0-50% de n-heptano/EA en 60 min). Se obtuvieron 6,68 g del

compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,50 (2 H, aromático), 4,70 (1 H, -O-C(-C)H-O-), 3,90 (3 H, $-OCH_3$), 2,54 (3 H, acetilo)

O2.071

1-{3-terc-Butil-4-metoxi-5-[3-(tetrahidropiran-2-iloxi)propoxi]fenil}etanona

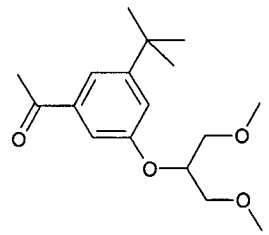


1-(3-terc-Butil-5-hidroxi-4-metoxifenil)etanona (O3.070; 6,9 g) y 2-(3-bromo-propoxi)tetrahidropirano (8,31 g) se disolvieron en DMF (80 ml), y se añadió hidruro de sodio (894 mg). Después de agitar a TA durante 5 horas, el disolvente se separó y el residuo se recogió con EA. La fase de EA se lavó con agua, se secó y se concentró. Se obtuvieron 12,7 g del compuesto del título en forma de un producto bruto con una purza suficiente.

^{1}H RMN (400 MHz, DMSO-d6) [ppm] (señales representativas): 4,57 (1 H, -O-C(-C)H-O-), 2,54 (3 H, acetilo)

O2.072

1-[3-terc-Butil-5-(2-metoxi-1-metoximetiletoxi)fenil]etanona

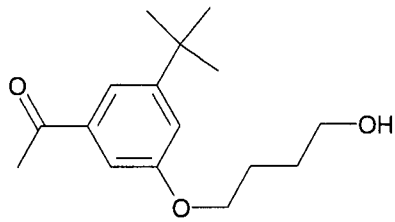


3-terc-Butil-5-(2-metoxi-1-metoximetiletoxi)benzoato de metilo (O5.072) se convirtió en el compuesto del título (1,65 g) de forma análoga a O4.043, O3.059 y O2.043. No se llevó a cabo cromatografía en la última etapa.

Tr de LC-MS: 1,63 min [M+H$^+$]: 295,1 (met. a)

O2.073

1-[3-terc-Butil-5-(4-hidroxibutoxi)fenil]etanona

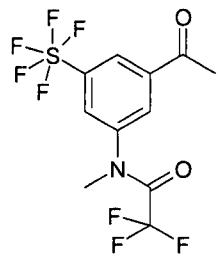


3-terc-Butil-5-(4-hidroxibutoxi)-N-metoxi-N-metilbenzamida (O3.073; 3,47 g) se convirtió, se trató y se purificó de forma análoga a O2.043. La purificación utilizando gel de sílice se llevó a cabo como sigue: cartucho de 40 g, gradiente de 0-100% de n-heptano/EA en 60 min. Se obtuvieron 2,08 g del compuesto del título.

Tr de LC-MS: 0,92 min [M+H$^+$]: 265,1 (met. b)

O2.075

N-[3-Acetil-5-(pentafluorosulfanil)-fenil]-2,2,2-trifluoro-N-metil-acetamida

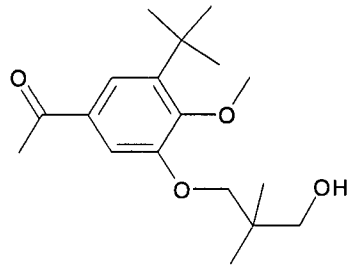


En un inserto de microondas, N-(3-acetil-5-pentafluorosulfanilfenil)-2,2,2-trifluoroacetamida (O3.075; 0,25 g) se disolvió en dimetoxietano absoluto (7,5 ml), se añadió carbonato de potasio en polvo y la mezcla se combinó con yodometano (80 µl). Subsiguientemente, la mezcla se calentó en el microondas hasta100°C durante 40 min. Una vez que N-(3-acetil-5-pentafluorosulfanilfenil)-2,2,2-trifluoroacetamida adicional (4 x 250 mg) se había convertido de la manera descrita, las cinco tandas se trataron juntas, mediante decantación en carbonato de potasio en ácido clorhídrico 1 N con enfriamiento con hielo. Después de lavar repetidamente el residuo de carbonato de potasio con dimetoxietano, la fase acuosa se extrajo cinco veces con acetato de etilo. Los extractos reunidos se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó kediante HPLC preparativa (met. A). Las fracciones con contenido en producto se reunieron, se liberaron del acetonitrilo y se extrajeron cinco veces con acetato de etilo. Los extractos reunidos se secaron sobre sulfato de magnesio, se filtraron y se concentraron. Se obtuvieron 1,03 g del compuesto deseado.

Tr de LC-MS: 1,62 min [M+H$^+$]: 372,0 (met. a)

O2.085

1-[3-terc.-Butil-5-(3-hidroxi-2,2-dimetilpropoxi)-4-metoxifenil]etanona

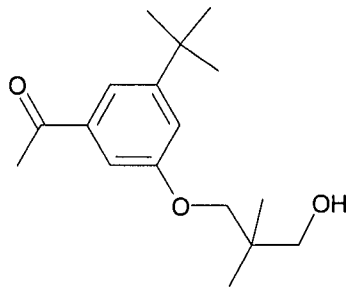


1-(3-terc-Butil-5-hidroxi-4-metoxifenil)etanona (O3.070; 2,00 g) y acetato de 3-bromo-2,2-dimetilpropilo (2,54 g) se disolvieron en DMF (15 ml), y se añadió carbonato de cesio (3,69 g). Después de agitar a 150°C y a máx. 15 bar en un microondas durante 2,5 h, se añadieron 0,5 eq. Adicionales del bromuro y la mezcla se dispuso en el microondas a 150°C durante 2 h adicionales. Después, la mezcla se concentró mediante evaporación rotatoria y el residuo se repartió entre DCM y agua. La fase en DCM se separó, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 120 g, gradiente de 0-50% de n-heptano/MtB-éter en 60 min). Se obtuvieron 1,17 g del compuesto del título.

Tr de LC-MS: 1,92 min [M+H$^+$]: 351,1 (met. a)

O2.086

1-[3-terc-Butil-5-(3-hidroxi-2,2-dimetilpropoxi)fenil]etanona

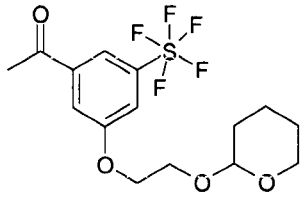


3-terc-Butil-5-(3-hidroxi-2,2-dimetilpropoxi)-N-metoxi-N-metilbenzamida (O3.086; 910 mg) se convirtió, se trató y se purificó de forma análoga a O2.059. Se obtuvieron 388 mg del compuesto del título.

LC-MS rt: 1,62 min [M+H]$^+$: 372,0 (met. a)

O2.090

1-{3-(Pentafluorosulfanil)-5-[2-(tetrahidro-piran-2-iloxi)-etoxi]-fenil}-etanona

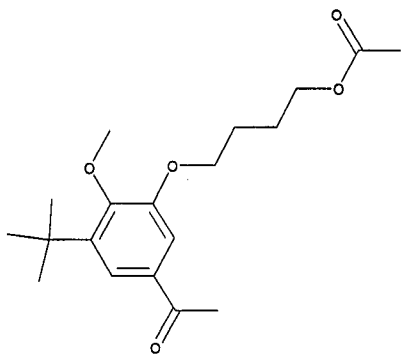


1-[3-Hidroxi-5-(pentafluorosulfanil)fenil]etanona (O3.050; 700 mg) y 2-(2-bromoetoxi)tetrahidropirano (670 mg) se disolvieron en DMF (15 ml), y se añadió hidruro de sodio (77 mg). Después de agitar a TA durante 2 h, la mezcla se calentó hasta 50°C durante 4 h y se dejó reposar durante el fin de semana. Después se separó la DMF y el residuo se recogió en EA. La fase en EA se lavó con agua, se secó, se filtró y se concentró. El producto bruto se purificó utilizando gel de sílice (100 g, n-heptano/EA 4:1). Se obtuvieron 813 mg del compuesto del título.

^{1}H-RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,87 (1 H), 7,80 (1 H), 7,71 (1 H), 4,66 (1 H, -O-C(-C)H-O-), 4,35 (2 H), 2,66 (3 H)

O2.095

Acetato de 4-(5-acetil-3-terc-butil-2-metoxifenoxi)butilo

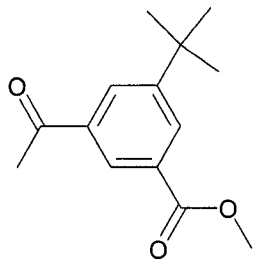


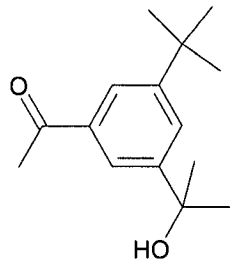
1-(3-terc-Buti-5-hidroxi-4-metoxifenil)etanona (O3.070; 6,9 g) se convirtió y se trató de forma análoga a O2.071. El bromuro utilizado era acetato de 4-bromobutilo (7,27 g). Se obtuvieron 10,5 g del compuesto del título.

LC-MS rt: 1,14 min [M+H]$^+$: 337,1 (met. b)

O2.100

3-Acetil-5-terc-butilbenzoato de metilo y 1-[3-terc-butil-5-(1-hidroxi-1-metiletil)-fenil]etanona





5-terc-Butil-N-metoxi-N-metilisoftalamidato de metilo (O3.100; 10,4 g) se disolvió a TA en THF (150 ml) bajo argón. Después se añadió gota a gota bromuro de metilmgnesio (19 ml; 3 M en dietil-éter) a 0°C mientras se agitaba. Después de 10 min, se retiró el baño de hielo y la mezcla se agitó a TA durante 3,5 h. Luego, la mezcla se combinó con ácido clorhídrico 1 N y agua mientras se enfriaba con hielo. La fase acuosa se extrajo tres veces con EA y las fases en EA reunidas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó utilizando gel de sílice. Se obtuvieron 7,0 g de 3-acetil-5-terc-butilbenzoato de metilo y 550 mg de 1-[3-terc-butil-5-(1-hidroxi-1-metiletil)fenil]etanona.

3-Acetil-5-terc-butilbenzoato de metilo

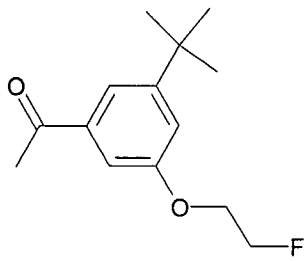
LC-MS rt: 1,13 min [M+H]$^+$: 235,2 (met. b)

1-[3-terc-Butil-5-(1-hidroxi-1-metiletil)fenil]etanona

LC-MS rt: 1,03 min [M+H]$^+$-OH: 217,2 (met. b)

O2.105

1-[3-tert-Butyl-5-(2-fluoroethoxy)phenyl]ethanone ZSI2.060



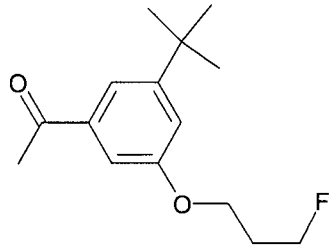
1-(3-terc-Butil-5-hidroxifenil)etanona (O3.106; 500 mg) se disolvió en DMF (10 ml), y se añadió 1-bromo-2-fluoroetano (195 µl) mientras se agitaba. Se añadió hidruro de sodio (80 mg) a TA. Después de agitar a TA durante 3 h, la mezcla se dejó reposar durante una noche y luego se añadió hidruro de sodio adicional (20 mg) y la mezcla se agitó durante 2 h adicionales. Luego se añadió agua y la mezcla se concentró hasta sequedad. El residuo se recogió en EA y se lavó tres veces con agua. La fase en EA se secó sobre sulfato de magnesio, se filtró y se concentró. Se obtuvieron

600 mg del compuesto del título.

LC-MS rt: 1,13 min [M+H]$^+$: 239,1 (met. b)

O2.106

1-[3-terc-Butil-5-(3-fluoropropoxi)fenil]etanona

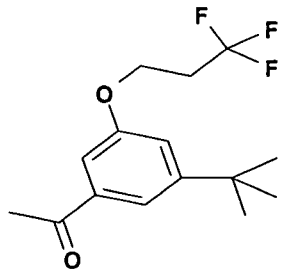


1-(3-terc-Butil-5-hidroxifenil)etanona (O3.106; 500 mg) se hizo reaccionar con 1-bromo-3-fluoropropano (239 µl) y se trató de forma análoga a O2.105. Se obtuvieron 630 mg del compuesto del título.

LC-MS rt: 1,16 min [M+H]$^+$: 253,2 (met. b)

O2.107

1-[3-terc-Butil-5-(3,3,3-trifluoro-propoxi)-fenil]-etanona

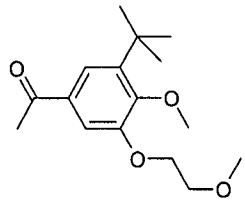


A una solución de 1-(3-terc-butil-5-hidroxifenil)etanona (O3.106; 300 mg, 1,56 mmol), 3,3,3-trifluoropropanol (178 mg, 1,56 mmol) y trifenilfosfina (409 mg, 1,56 mmol) en diclorometano (5 ml) a TA se añadió una solución de azodicarboxilato de di(4-clorobencilo) (573 mg, 1,56 mmol) en diclorometano (1 ml). La mezcla se agitó durante 5 días y luego se filtró. El disolvente se separó y el residuo se purificó mediante cromatografía de resolución rápida (n-heptano:acetato de etilo). Rendimiento: 170 mg, 38%.

Tr de LC-MS: 1,14 min [M+H$^+$]: 289,2 (met. b)

O2.110

1-[3-terc-Butil-4-metoxi-5-(2-metoxi-etoxi)-fenil]-etanona

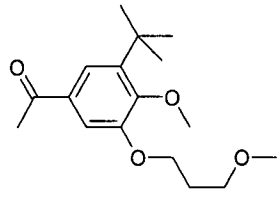


Se disolvieron 1-(3-terc-butil-5-hidroxi-4-metoxi-fenil)-etanona (O3.070; 2,00 g) y 1-bromo-2-metoxi-etano (1,5 g) en DMF (20 ml) y se añadió hidruro sódico (259 mg). Después de agitar durante 3 h a TA, la mezcla se dejó en reposo durante una noche. Después, la DMF se retiró y el residuo se recogió en EA. La fase de EA se lavó con agua, se secó, se filtró y se concentró. El residuo se purificó usando gel de sílice (cartucho de 80 g, gradiente de 0-40% de n-heptano/EA en 60 min). Se obtuvieron 1,17 g del compuesto del título.

Tr de LC-MS: 1,03 min [M+H$^+$]: 281,1 (met. b)

O2.111

1-[3-terc-Butil-4-metoxi-5-(3-metoxi-propoxi)-fenil]-etanona

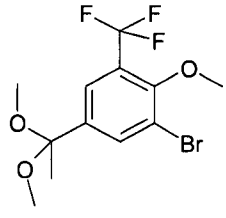


1-(3-terc-Butil-5-hidroxi-4-metoxifenil)etanona (O3.070; 2,00 g) y 1-bromo-3-metoxipropano (1,65 g) se convirtieron, se trataron y se purificaron de forma análoga a O2.110. Se obtuvieron 1,50 g del compuesto del título.

Tr de LC-MS: 1,09 min [M+H$^+$]: 295,2 (met. b)

O3.004

1-Bromo-5-(1,1-dimetoxi-etil)-2-metoxi-3-trifluorometil-benceno



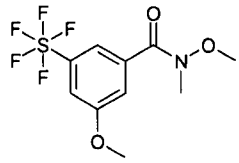
1-(3-Bromo-4-hidroxi-5-trifluorometilfenil)etanona (O4.004; 6,8 g) se disolvió en metanol (50 ml) y se mezcló sucesivamente con ácido DL-10-canfosulfónico (111 mg) y ortoformiato de trimetilo (8 ml). Después de agitar a TA durante 2 h, se añadieron DMF (75 ml), carbonato de potasio (4,98 g) y luego, lentamente, mientras

se enfriaba con hielo, yodometano (3 ml). Después de agitar a TA durante 4 h, la mezcla de reacción se dejó reposar durante una noche y combinó con n-heptano/agua, y la fase orgánica se separó. La fase acuosa se extrajo sacudiendo una vez más con n-heptano, y las fases orgánicas reunidas se secaron luego sobre sulfato de magnesio, se filtraron y se concentraron. Se obtuvieron 7 g del compuesto del título en suficiente pureza.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,90 (1 H), 7,62 (1 H), 3,89 (3 H), 3,10 (6 H), 1,49 (3 H)

O3.007

3,N-Dimetoxi-N-metil-5-(pentafluorosulfanil)-benzamida

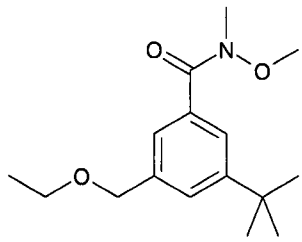


Se disolvió 3-metoxi-5-(pentafluorosulfanil)-benzoato de metilo (O4.007; 2,5 g) en THF absoluto (65 ml) y se añadió hidrocloruro de N,O-dimetilhidroxilamina (1,2 g). Después, la mezcla se enfrió a -15°C y se añadió gota a gota una solución de bromuro de isopropilmagnesio (13,59 ml, 2 M en THF). Después de agitar durante 20 min, el baño de refrigeración se retiró y la agitación se continuó durante 1 h a TA. Después, se añadió una solución de cloruro de amonio y la fase acuosa se extrajo tres veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El producto en bruto, así obtenido, seguía conteniendo reaccionante significativo y, por lo tanto, se convirtió y se trató de nuevo como se ha descrito anteriormente. En el residuo ya no quedaba presente reaccionante. La purificación se realizó por medio de HPLC preparativa (met. A). Las fracciones que contenían producto se combinaron, se liberaron del acetonitrilo y la fase acuosa se extrajo tres veces con EA. Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. Se obtuvieron 1,78 g del compuesto deseado.

^{1}H RMN (400 MHz, $CDCl_3$) [ppm]: 7,70 (1 H), 7,37 (1 H), 7,24 (1 H + $CDCl_3$), 3,89 (3 H), 3,56 (3 H)

O3.008

3-terc-Butil-5-etoximetil-N-metoxi-N-metil-benzamida

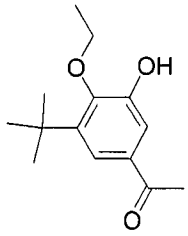


De forma análoga a O3.043, ácido 3-terc-butil-5-etoximetil-benzoico (O4.008; 1,15 g) se convirtió en el cloruro de ácido (1,24 g) y luego el cloruro de 3-terc-butil-5-etoximetilbenzoílo obtenido se convirtió adicionalmente. Se obtuvieron 354 mg del compuesto del título.

Tr de LC-MS: 3,32 min [M+H$^+$]: 280,2 (met. d)

O3.010

1-(3-terc-Butil-4-etoxi-5-hidroxi-fenil)-etanona

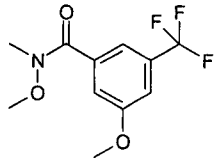


1-Bromo-3-terc-butil-5-(1,1-dimetoxi-etil)-2-etoxi-benceno (O4.010; 19,68 g) se convirtió de forma análoga a O3.070. Se obtuvieron 5,15 g del compuesto del título.

Tr de LC-MS: 0,972 min [M+H$^+$]: 237,1 (met. b)

O3.014

3,N-Dimetoxi-N-metil-5-trifluorometil-benzamida



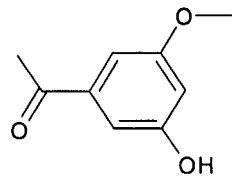
3-Metoxi-5-trifluorometilbenzoato de metilo (O4.014, 1 g) y N,O-dimetilhidroxilamina (416 mg) se cargaron inicialmente en THF (30 ml). Después de ello, la mezcla se enfrió hasta -15°C, y se añadió gota a gota cloruro de isopropilmagnesio (3,2 ml; 2 M en THF) en el espacio de 10 min. La mezcla se agitó a -15°C durante otros 20 min antes de retirar el baño de refrigeración. Al cabo de 3 h, la mezcla se enfrió de nuevo hasta -15°C y se añadió cloruro de isopropilmagnesio adicional (3,2 ml). Después de haber separado el baño de refrigeración, la mezcla se agitó a TA

durante otra hora, luego se combinó con solución de cloruro de amonio al 20% y se extrajo tres veces con EA. Las fases en EA combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó utilizando gel de sílice (cartucho dfe 50 g, DCM como eluyente). Se obtuvieron 465 mg del compuesto del título, así como 427 mg de reaccionante.

Tr de LC-MS: 1,36 min [M+H$^+$]: 264,0 (met. a)

O3.033

1-(3-Hidroxi-5-metoxifenil)etanona

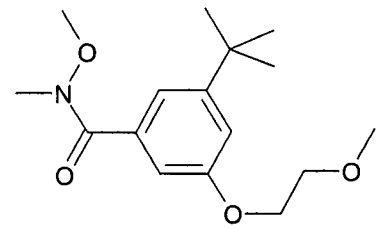


1-(3,5-Dihidroxifenil)etanona (3 g) y yoduro de metilo (2,80 g) se disolvieron en DMF (40 ml), y se añadió hidruro de sodio (568 mg). Después de agitar a TA durante 2 h, la DMF se separó. El residuo se recogió en EA y se lavó con agua, se secó, se filtró y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 89 g, 0-50% de n-heptano/EA en 30 min). Se obtuvieron 1,12 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 9,8 (1 H); 6,93 (2 H); 6,58 (1 H); 3,76 (3 H); 2,50 (3 H + DMSO)

O3.043

3-terc-Butil-N-metoxi-5-(2-metoxietoxi)-N-metilbenzamida



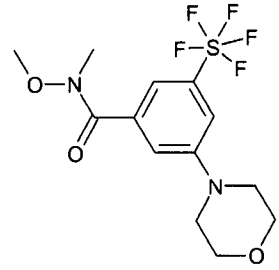
Se disolvió ácido 3-terc-butil-5-(2-metoxietoxi)benzoico (O4.043; 1,9 g) en cloruro de tionilo (10,9 ml), se mantuvo a la temperatura de reflujo durante 2 h y después se concentró. El cloruro de 3-terc-butil-5-(2-metoxietoxi)benzoílo resultante (2,04 g) se disolvió en DCM (20 ml) y se mezcló con dimetilhidroxilamina (734 mg), después se añadió base de Hünig (1,37 ml) y la mezcla se agitó a TA durante 1 h. Después, la mezcla se secó, el residuo se recogió en EA y la mezcla se lavó cuatro veces con agua, se secó sobre sulfato de magnesio, se filtró y se concentró por evaporación

rotatoria. El residuo se purificó usando gel de sílice (cartucho de 40 g, gradiente de 0-50% de n-heptano/EA en 40 min). Se obtuvieron 1,36 g del compuesto del título.

Tr de LC-MS: 1,43 min [M+H$^+$]: 296,3 (met. a)

O3.044

N-Metoxi-N-metil-3-morfolin-4-il-5-(pentafluorosulfanil)-benzamida

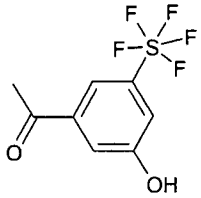


3-Amino-N-metoxi-N-metil-5-(pentafluorosulfanil)benzamida (O5.075; 6,3 g) se disolvieron en DMF (80 ml), y se añadieron carbonato de cesio (10,1 g), yoduro de sodio (0,62 g) y bis(2-bromoetil)-éter (19,37 g). La mezcla se dividió entre 10 recipientes de microondas, cada uno de los cuales se calentó hasta 130°C durante 3 h. Subsiguientemente, las tandas se combinaron y se liberaron de disolvente. El residuo se recogió en EA y se lavó con agua. La fase en EA se secó y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 120 g, gradiente de 0-100% de n-heptano/EA en 30 min). Se obtuvieron 2,48 g del compuesto del título.

Tr de LC-MS: 1,41 min [M+H$^+$]: 377,0 (met. a)

O3.050

1-[3-Hidroxi-5-(pentafluorosulfanil)fenil]etanona



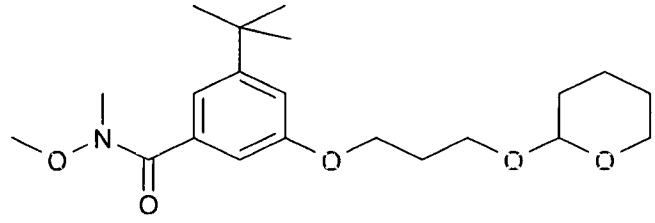
1-[3-Amino-5-(pentafluorosulfanil)fenil]etanona (O4.050; 3,00 g) se disolvió en ácido sulfúrico acuoso al 35% (25 ml) mientras se calentaba. La solución se enfrió hasta -5°C y se añadió gota a gota una solución de nitrito de sodio (780 mg) en 15 ml de agua en el espacio de 10 min. Después de 40 min a -5°C, se retiró el baño de refrigeración y la mezcla sde calentó hasta 100°C durante 2 h. Después del enfriamiento, la mezcla se extrajo dos veces con EA. Las fases en EA combinadas

se lavaron con solución saturada de hidrógeno-carbonato de sodio, se secaron, se filtraron y se concentraron. El residuo se purificó utilizando gel de sílice (cartucho de 80 g cartridge, gradiente de 0-100% de n-heptano/MTB-éter en 40 min). Se obtuvieron 1,62 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 10,71 (1 H), 7,73 (1 H), 7,59 (1 H), 7,47 (1 H), 2,61 (3 H)

O3.059

3-terc-Butil-N-metoxi-N-metil-5-[3-(tetrahidro-piran-2-iloxi)-propoxi]-benzamida

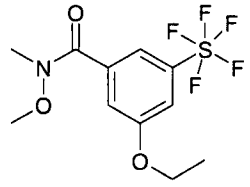


Se disolvieron ácido 3-terc-butil-5-[3-(tetrahidro-piran-2-iloxi)-propoxi]-benzoico (O4.059; 4,90 g) e hidrocloruro de N,O-dimetilhidroxilamina (1,42 g) en DMF (80 ml) y se mezclaron con base de Hünig (4,31 ml) y TOTU (4,78 g). Después de agitar durante 2 h, la mezcla se dejó en reposo durante una noche. Después, la DMF se retiró, la mezcla se repartió entre EA y solución saturada de hidrógeno-carbonato sódico, y la fase de EA se separó, se secó sobre sulfato de magnesio, se filtró y se concentró. Se obtuvieron 5,49 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,12 (1 H), 7,01 (1 H), 6,90 (1 H), 4,56 (1 H, -O-C(-C)H-O-), 4,06 (2 H), 3,57 (3 H), 3,22 (3 H)

O3.062

3-Etoxi-N-metoxi-N-metil-5-(pentafluorosulfanil)-benzamida

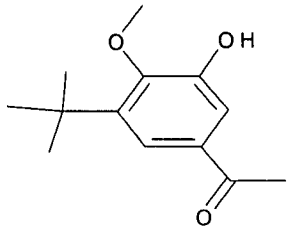


3-Etoxi-5-(pentafluorosulfanil)benzoato de etilo (O4.062; 4,80 g) se convirtió y se trató de forma análoga a O3.007. El residuo se purificó utilizando gel de sílice (cartucho de 120 g, gradiente de 20-100% de n-heptano/MTB-éter en 60 min). Se obtuvieron 2,80 g del compuesto del título.

Tr de LC-MS: 1,60 min [M+H$^+$]: 336,0 (met. a)

O3.070

1-(3-terc-Butil-5-hidroxi-4-metoxi-fenil)-etanona

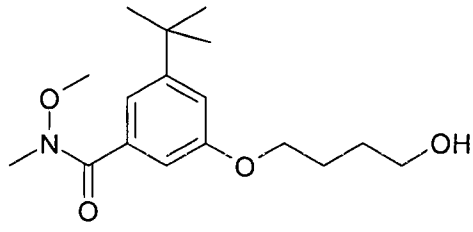


Se disolvió 1-bromo-3-terc-butil-5-(1,1-dimetoxi-etil)-2-metoxi-benceno (O4.070; 36,3 g) en THF (1 l), en una atmósfera de argón a -75°C, se añadió gota a gota n-butil-litio (52,6 ml; 2,5 M en hexano) y la mezcla se agitó durante otros 30 min. Después, se añadió gota a gota borato de trimetilo (37,3 ml) y durante 2 h se dejó que la mezcla volviera a la TA. Subsiguientemente, se añadieron sucesivamente hidróxido sódico (4,4 g, disuelto en 10 ml de agua) y una solución de peróxido de hidrógeno (62,3 ml; al 35% en agua). Después de agitar durante 2 h a TA, la mezcla se dejó en reposo durante una noche. Después, se añadieron agua y EA y la mezcla se acidificó con ácido clorhídrico. Después de separar la fase de EA, ésta se secó sobre sulfato de magnesio y se concentró. El residuo se purificó usando gel de sílice (cartucho de 330 g, gradiente de 0-50% de n-heptano/EA en 60 min). Se obtuvieron 14 g del compuesto del título.

Tr de LC-MS: 0,90 min [M+H$^+$]: 223,1 (met. b)

O3.073

3-terc-Butil-5-(4-hidroxibutoxi)-N-metoxi-N-metilbenzamida

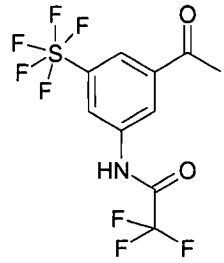


Ácido 3-terc-butil-5-(4-hidroxibutoxi)benzoico (O4.073; 4,13 g) se convirtió y se trató de forma análoga a O3.059. Para la purificación ulterior, la cromatografía se efectuó utilizando gel de sílice como sigue: cartucho de 80 g, gradiente de 0-100% de n-heptano/EA en 60 min. Se obtuvieron 3,47 g del compuesto del título.

Tr de LC-MS: 0,66 min [M+H$^+$]: 310,3 (met. b)

O3.075

N-(3-Acetil-5-pentafluorosulfanilfenil)-2,2,2-trifluoroacetamida

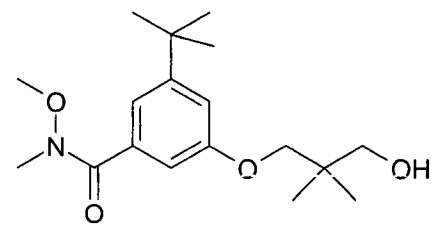


N-Metoxi-N-metil-3-(pentafluorosulfanil)-5-(2,2,2-trifluoroacetilamino)benzamida (O4.075; 1,65 g) se disolvió en THF (25 ml). A 0°C, se añadió bis(trimetilsilil)amida de litio (0,9 ml) mientras se agitaba. Después de 30 min, se añadió gota a gota bromuro de metilmagnesio (3,5 ml, 3 M en dietil-éter). Después de haber finalizado la adición, se retiró el baño de hielo y la mezcla se agitó a TA durante 2 h. Mientras se enfriaba, se añadieron entonces ácido clorhídrico 1 N, agua y EA. Después de separar la fase orgánica, la fase acuosa se extrajo dos veces más con EA. Las fases en EA combinadas se secaron con sulfato de magnesio, se filtraron y se concentraron. El producto bruto es una mezcla de N-(3-acetil-5-pentafluorosulfanil-fenil)-2,2,2-trifluoroacetamida y 1-[3-amino-5-(pentafluorosulfanil)fenil]etanona y, así, el producto bruto (1,3 g) se recogió en cloruro de metileno (60 ml) y se mezcló con trietilamina (155 µl). Después de ello, se añadió anhídrido trifluoroacético (160 µl) mientras se agitaba. Después de agitar a TA durante 3 h, se añadieron agua y solución saturada de hidrógeno-carbonato de sodio, las fases se separaron y la fase en DCM se lavó tres veces más con agua. La fase en DCM se secó con sulfato de magnesio, se filtró y se concentró. Se obtuvieron 1,3 g del compuesto del título.

Tr de LC-MS: 1,61 min [M+H$^+$]: 358,0 (met. a)

O3.086

3-terc-Butil-5-(3-hidroxi-2,2-dimetilpropoxi)-N-metoxi-N-metilbenzamida



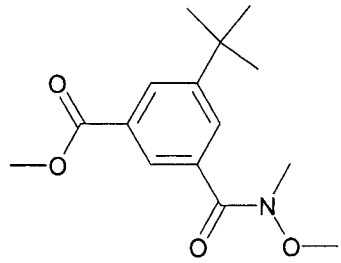
Ácido 3-terc-Butil-5-(3-hidroxi-2,2-dimetilpropoxi)benzoico (O4.086; 940 mg) se convirtió y se trató de forma análoga a O3.059. Se obtuvieron 910 mg del

compuesto del título.

Tr de LC-MS: 1,50 min [M+H$^+$]: 324,1 (met. a)

O3.100

5-terc-Butil-N-metoxi-N-metilisoftalamidato de metilo

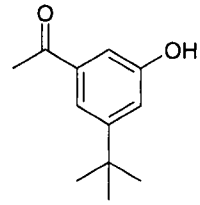


5-terc-Butilisoftalato de monometilo (10,0 g) se convirtió, se trató y se purificó de forma análoga a O3.043. Se obtuvieron 10,6 g del compuesto del título.

Tr de LC-MS: 1,06 min [M+H$^+$]: 280,2 (met. b)

O3.106

1-(3-*terc*-Butil-5-hidroxifenil)etanona

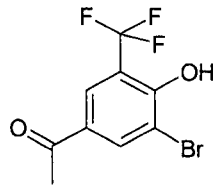


Ácido *m*-cloroperbenzoico (382 g, 2,21 mol) se añadió a una solución de 1,3-bisacetil-5-*terc*-butilbenceno (O4.106; 169 g, 776 mmol) en diclorometano (1,7 l). La suspensión resultante se calentó hasta la temperatura de reflujo durante 24 h. Una vez se hubo enfriado la suspensión, los sólidos se separaron mediante filtración y el filtrado se mezcló con solución acuosa saturada de $NaHSO_3$ (500 ml). Las fases se separaron, la fase orgánica se secó ($MgSO_4$) y el disolvente se separó a presión reducida. El residuo se disolvió en THF (500 ml) y se mezcló con hidróxido de litio (34,9 g, 1,46 mol). Después de 4 h a TA, se añadió solución acuosa de hidróxido de sodio (1 M, 500 ml) y la mezcla se lavó con MtB-éter (3 × 500 ml). La fase acuosa se acidificó (pH 3) con HCl (1 M), y se extrajo con EA (3 × 500 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), y el disolvente se separó a presión reducida. El producto bruto se purificó mediante HPLC preparativa (met. C). El producto se obtuvo en forma de un aceite incoloro que cristalizó lentamente (36,5 g).

Tr de LC-MS: 1,30 min [M+H$^+$]: 193 (met. a)

O4.004

1-(3-Bromo-4-hidroxi-5-trifluorometil-fenil)-etanona

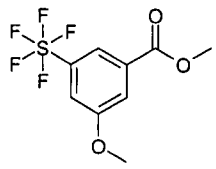


1-(4-Hidroxi-3-trifluorometilfenil)etanona (5 g) se cargó inicialmente en acetonitrilo (150 ml) a TA mientras se agitaba y se enfrió hasta -10°C. A esta temperatura, se añadió gota a gota N-bromosuccinimida (4,5 g, disueltos en 100 ml de acetonitrilo). Luego se retiró el baño de refrigeración y la mezcla se agitó durante 5 h adicionales. Después de reposar durante una noche, se separaron ¾ del disolvente y el residuo se mezcló con n-heptano/agua. La fase orgánica se separó y se lavó una vez con solución de tiosulfato de sodio al 5% y una vez con agua. El precipitado formado se separó por filtración con succión, se lavó y se secó. Se obtuvieron 6,9 g del compuesto del título en una pureza suficiente.

Tr de LC-MS: 1,35 min [M+H$^+$]: 283,0 (met. a)

O4.007

3-Metoxi-5-(pentafluorosulfanil)-benzoato de metilo



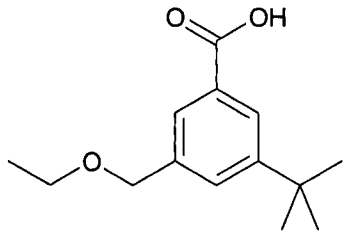
Se disolvió ácido 3-hidroxi-5-(pentafluorosulfanil)-benzoico (O5.007; 3,0 g) en DMF absoluta (75 ml). Mientras se agitaba, se añadió luego yodometano (3,6 ml), seguido de carbonato potásico (6,3 g) finamente en polvo. Después de agitar durante 5 horas a 40°C, la mezcla se enfrió y se combinó con agua (250 ml). La mezcla se extrajo luego cuatro veces con éter (100 ml). Los extractos combinados se lavaron en cada caso una vez con una solución 1 N de hidróxido sódico (75 ml) y una vez con agua (100 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron. Se obtuvieron 2,9 g del compuesto deseado.

^{1}H RMN (400 MHz, $CDCl_3$) [ppm]: 8,00 (1 H), 7,70 (1 H), 7,47 (1 H), 3,96 (3 H), 3,90

(3 H)

O4.008

Ácido 3-terc-butil-5-etoximetil-benzoico

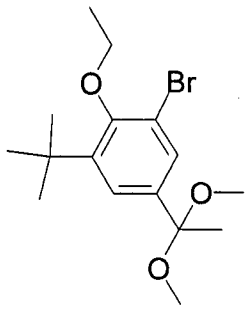


3-terc-Butil-5-etoximetil-benzoato de metilo (O5.008; 1,18 g) se convirtió de forma análoga a O4.043. Sin embargo, el producto bruto obtenido se purificó posteriormente utilizando gel de sílice (cartucho de 50 g, gradiente de 0-50% de n-heptano/EA en 30 min). Se obtuvieron 1,15 g del compuesto del título.

^{1}H RMN (400 MHz, DMSO-d_6) [ppm]: 12,90 (1 H), 7,86 (1 H), 7,73 (1 H), 7,57 (1 H), 4,50 (2 H), 3,50 (1 H), 1,30 (9 H), 1,16 (3 H)

O4.010

1-Bromo-3-terc-butil-5-(1,1-dimetoxi-etil)-2-etoxi-benceno

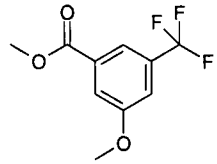


2-Bromo-6-terc-butil-4-(1,1-dimetoxi-etil)-fenol (20 g; para la síntesis véase el documento CA 02515715) con yoduro de etilo de forma análoga a las condiciones de O4.070. Se obtuvieron 19,67 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,46 (1 H), 7,33 (1 H), 4,03 (2 H), 3,06 (6 H), 1,43 (3 H), 1,38 (3 H), 1,35 (9 H)

O4.014

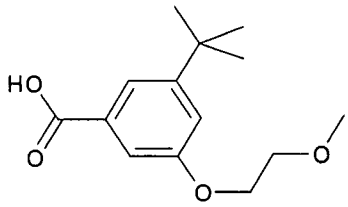
3-Metoxi-5-trifluorometil-benzoato de metilo



Ácido 3-hidroxi-5-trifluorometilbenzoico (2 g) se cargó inicialmente a TA en DMF (15 ml) mientras se agitaba, y se mezcló gota a gota con yoduro de metilo (3,0 ml). Después de añadir carbonato de potasio (5,6 g), la mezcla se agitó durante 5 h y se dejó reposar durante una noche. Luego se mezcló con agua y se extrajo tres veces con MTB-éter. Las fases en MTB-éter combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. Se obtuvieron 2,29 g del compuesto del título.
^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,76 (1 H), 7,70 (1 H), 7,55 (1 H), 3,91 (3 H), 3,89 (3 H)

O4.043

Ácido 3-terc-butil-5-(2-metoxietoxi)benzoico

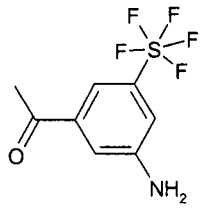


Se disolvió 3-terc-butil-5-(2-metoxietoxi)benzoato de metilo (O5.043; 2,0 g) en metanol (30 ml) y THF (60 ml) y se añadió una solución de hidróxido de litio (30 ml, 1 M en agua). La mezcla se calentó a 40°C y se agitó durante 3 h. Después, los disolventes orgánicos se retiraron y la fase acuosa se ajustó a un valor de pH de 3 con ácido clorhídrico 1 N. La mezcla se extrajo con EA, se secó, se filtró y se concentró. Se obtuvieron 1,9 g del compuesto del título.

Tr de LC-MS: 1,40 min [M+H$^+$-H_2O]: 235,3 (met. a)

O4.050

1-[3-Amino-5-(pentafluorosulfanil)-fenil]-etanona



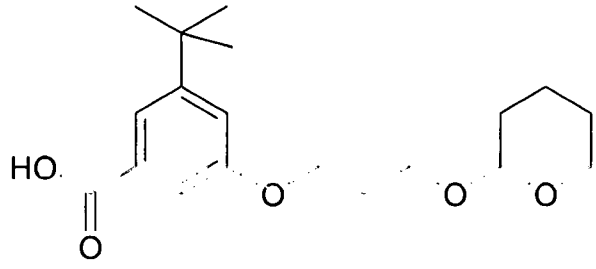
N-(3-Acetil-5-pentafluorosulfanilfenil)-2,2,2-trifluoroacetamida (O3.075; 9,4 g) se

mezcló con ácido sulfúrico semiconcentrado (200 ml), y se añadió DCM (15 ml). Después de agitar a 100°C durante 7 h, la mezcla se dejó reposar durante una noche. Después, la mezcla se añadió a hielo-agua y se extrajo EA. Las fases de EA combinadas se lavaron con solución saturada de hidrógeno-carbonato de sodio, se secaron sobre sulfato de magnesio, se filtraron y se concentraron mediante evaporación rotatoria. Se obtuvieron 6,36 g del compuesto del título.

Tr de LC-MS: 1,38 min [M+H$^+$]: 262,0 (met. a)

O4.059

Ácido 3-terc-butil-5-[3-(tetrahidro-piran-2-iloxi)-propoxi]-benzoico

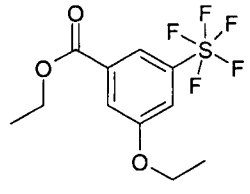


Se disolvió 3-terc-butil-5-[3-(tetrahidro-piran-2-iloxi)-propoxi]-benzoato de metilo (O5.059; 5,37 g) en metanol (80 ml) y THF (160 ml) y se añadió una solución de hidróxido de litio (61,28 ml, 1 M en agua). Después de agitar durante 2 h a 40°C, la mezcla se secó y el residuo se recogió con agua y se liofilizó. El producto obtenido se agitó con DCM, se filtró y se secó. Se obtuvieron 4,9 g de producto.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,52 (1 H), 7,26 (1 H), 6,80 (1 H), 4,57 (1 H, -O-C(-C)H-O-), 4,02 (2 H)

O4.062

3-Etoxi-5-(pentafluorosulfanil)-benzoato de etilo

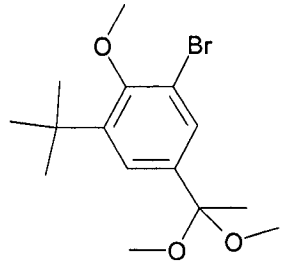


Ácido 3-hidroxi-5-(pentafluorosulfanil)benzoico (O5.007; 4,76 g) se hizo reaccionar con yoduro de etilo (7,27 ml) y se trató de forma análoga a O4.007. Se obtuvieron 4,80 g del compuesto del título.

Tr de LC-MS: 1,97 min [M+H$^+$]: 321,0 (met. a)

O4.070

1-Bromo-3-terc-butil-5-(1,1-dimetoxi-etil)-2-metoxi-benceno

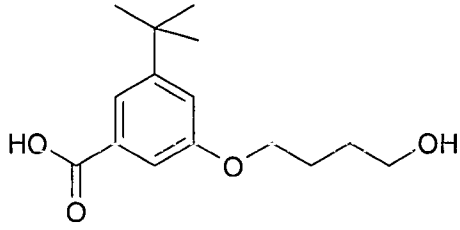


1-Bromo-3-terc-butil-5-(1,1-dimetoxi-etil)-2-metoxi-benceno se sintetizó de forma análoga a la solicitud de patente CA 02515715.

^{1}H RMN (500 MHz, DMSO-d6) [ppm]: 7,47 (1 H), 7,33 (1 H), 3,85 (3 H), 3,07 (6 H), 1,43 (3 H), 1,35 (9 H)

O4.073

Ácido 3-terc-butil-5-(4-hidroxibutoxi)benzoico

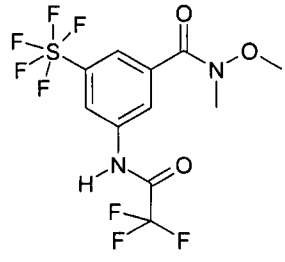


3-terc-Butil-5-hidroxibenzoato de metalo (O6.043; 3,3 g) se hizo reaccionar con acetato de 4-bromobutilo (3,71 g) y se trató de forma análoga a O5.043. El producto bruto se hidrolizó directamente, de forma análoga a O4.086, con hidróxido de litio para dar el compuesto del título (4,13 g).

Tr de LC-MS: 0,84 min [M+H$^+$]: 267,1 (met. b)

O4.075

N-Metoxi-N-metil-3-(pentafluorosulfanil)-5-(2,2,2-trifluoro-acetilamino)-benzamida



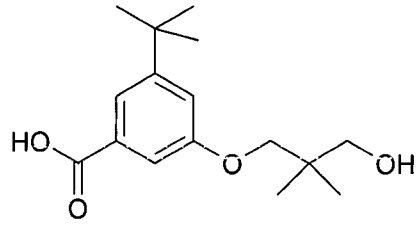
3-Amino-N-metoxi-N-metil-5-pentafluorosulfanilbenzamida (O5.075; 1,45 g) se

disolvió en cloruro de metileno (15 ml) y, mientras se agitaba, se añadieron trietilamina (0,8 ml), seguido de anhídrido trifluoroacético (0,85 ml) con la exclusión de la humedad. Después de agitar a TA durante 3 h y de dejar reposar durante una noche, se añadieron agua y solución saturada de hidrógeno-carbonato de sodio, las fases se separaron y la fase en cloruro de metileno se lavó tres veces con agua, se secó sobre sulfato de magnesio, se filtró y se concentró. El producto obtenido (1,75 g) se utilizó en la etapa siguiente sin purificación adicional.

Tr de LC-MS: 1,53 min [M+H$^+$]: 403,0 (met. a)

O4.086

Ácido 3-*tero*-butil-5-(3-hidroxi-2,2-dimetilpropoxi)benzoico

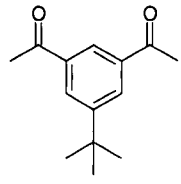


3-(3-Acetoxi-2,2-dimetilpropoxi)-5-*tero*-butilbenzoato de metilo (O5.086; 1 g) se disolvió en metanol/THF (15/30 ml), y se añadió solución de hidróxido de litio (11,89 ml, 1 M en agua). Después de agitar a 40°C durante 2 h, el disolvente orgánico se separó y el residuo se diluyó con agua y se ajustó a pH 3 con ácido clorhídrico 1 N. Después se extrajo con EA, y las fases orgánicas combinadas se secaron, se filtraron y se concentraron. Se obtuvieron 940 mg del compuesto del título.

Tr de LC-MS: 1,45 min [M+H$^+$]: 281,1 (met. a)

O4.106

1,3-Bisacetil-5-*tero*-butilbenceno



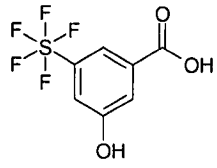
En un matraz de tres bocas de 4 l con un agitador mecánico, se añadió lentamente gota a gota una solución de 5-*tero*-butil-*N*,*N*'-dimetoxi-*N*,*N*'-dimetilisoftalamida (O5.106; 254 g, 560 mmol) en THF (700 ml) en el espacio de 2 h a bromuro de metilmagnesio (3 M en Et_2O, 1,49 l, 4,48 mol). La solución se enfrió durante la adición, de modo que la temperatura se mantuvo entre -10°C y +5°C. Tras

completarse la adición, se retiró el enfriamiento y la solución de reacción se agitó a TA durante 16 h. La solución de reacción se añadió luego lentamente a una mezcla enfriada de HCl (1 M, 500 ml) y hielo. Durante esta hidrólisis, el pH se mantuvo entre 3 y 6 mediante la adición de HCl concentrado. Tras completarse la adición, se añadió MTB-éter (1 l). Las fases se separaron y la fase acuosa se extrajo con MTB-éter (1 × 500 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), y el disolvente se separó a presión reducida. El producto se obtuvo en forma de un aceite incoloro (123 g).

Tr de LC-MS: 1,50 min [$M+H^+$]: 219 (met. a)

O5.007

Ácido 3-hidroxi-5-(pentafluorosulfanil)-benzoico

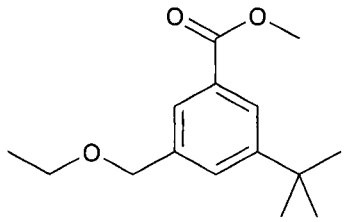


Ácido 3-amino-5-pentafluorosulfanilbenzoico (O6.007; 3,9 g) se disolvió en ácido sulfúrico al 35% (120 ml) y se enfrió hasta -5°C, y se añadió gota a gota una solución de nitrito de sodio (1,1 g) en agua (100 ml) en el espacio de 10 min. Después de 40 min, se añadió solución de nitrito adicional (2 ml), y otros 2 ml y 1 ml después de 20 min adicionales en cada caso. Después se retiró el baño de refrigeración y la mezcla se calentó hasta 100°C. Después de 5 h, la mezcla se enfrió y la solución se decantó. La solución transparente de carácter ácido se extrajo cinco veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El producto bruto se recristalizó en acetato de etilo/heptano. Se obtuvieron 3,6 g del compuesto deseado.

^{1}H RMN (400 MHz, DMSO-d_6) [ppm]: 10,72 (1 H); 7,71 (1 H); 7,57 (1 H); 7,46 (1H).

O5.008

3-terc-Butil-5-etoximetil-benzoato de metilo

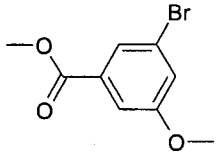


3-terc-Butil-5-hidroximetilbenzoato de metilo (2,0 g) se alquiló con yoduro de etilo de forma análoga a las condiciones de O5.043. Se obtuvieron 1,18 g del compuesto del título.

Tr de LC-MS: 3,81 min [M+H$^+$]: 250,2 (met. d)

O5.032

3-Bromo-5-metoxibenzoato de metilo

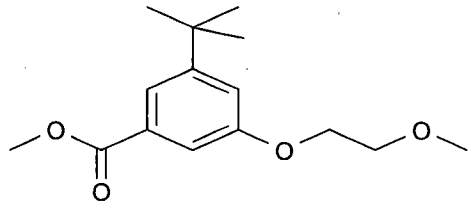


3-Bromo-5-hidroxibenzoato de metilo (O6.032; 2,52 g) se alquiló con yoduro de metilo y se trató de forma análoga a las condiciones de O5.043. Se obtuvieron 2,5 g del compuesto del título.

Tr de LC-MS: 1,58 min [M+H$^+$]: 245,0 (met. a)

O5.043

3-terc-Butil-5-(2-metoxietoxi)benzoato de metilo

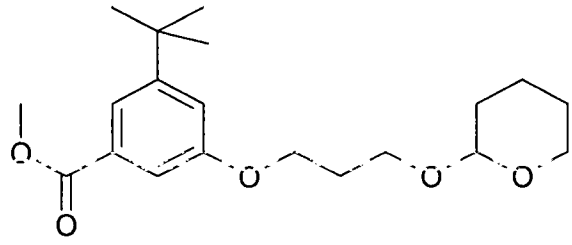


Se disolvieron 3-terc-butil-5-hidroxibenzoato de metilo (O6.043; 2,18 g) y 1-bromo-2-metoxietano (1,18 ml) en DMF (30 ml) y se añadió hidruro sódico (301 mg) mientras se agitaba. Después de agitar a TA durante 2 h, el disolvente se retiró. El residuo se recogió en EA y la mezcla se lavó con agua, se secó y se concentró. El residuo se purificó usando gel de sílice (cartucho de 80 g, gradiente de 0-30% de n-heptano/MtB éter en 60 min). Se obtuvieron 2,0 g del compuesto del título.

Tr de LC-MS: 1,69 min [M+H$^+$-OCH_3]: 235,2 (met. a)

O5.059

Éster metílico del ácido 3-terc-butil-5-[3-(tetrahidro-piran-2-iloxi)-propoxi]-benzoico

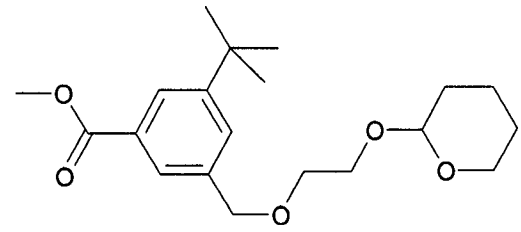


Se disolvieron 3-terc-butil-5-hidroxi-benzoato de metilo (O6.043; 3,22 g) y 2-(3-bromo-propoxi)-tetrahidro-pirano (4,14 g) en DMF (30 ml) y se añadió hidruro sódico (445 mg). Después de agitar durante 3 h a TA, la mezcla se dejó en reposo durante una noche. Después, la DMF se retiró y el residuo se recogió en EA, se lavó con agua, se secó, se filtró y se concentró. Se obtuvieron 5,37 g de producto.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,56 (1 H), 7,23 (1H), 7,19 (1 H), 4,57 (1 H, -O-C(-C)H-O-), 4,10 (2 H)

O5.063

3-terc-Butil-5-[2-(tetrahidropiran-2-iloxi)etoximetil]benzoato de metilo

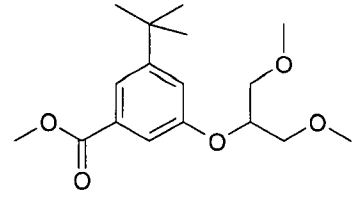


3-terc-Butil-5-hidroximetilbenzoato de metilo (3,5 g) se alquiló de forma análoga a O5.059 con 2-(2-bromoetoxi)tetrahidropirano (3,95 g). Sin embargo,para la purificación se llevó a cabo una cromatografía en gel de sílice (n-heptano/EA 4:1). Se obtuvieron 2,23 g del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d6) [ppm] (señales representativas): 7,87 (1 H); 7,76 (1 H); 7,63 (1 H); 4,60 (1 H, -O-C(-C)H-O-); 4,57 (2 H)

O5.072

3-terc-butil-5-(2-metoxi-1-metoximetiletoxi)benzoato de metilo

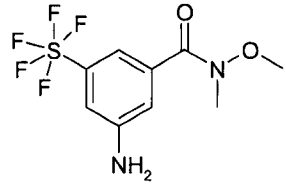


3-terc-Butil-5-hidroxibenzoato de metilo (O6.043; 2,28 g) y metanosulfonato de 2-metoxi-1-metoximetiletilo (2,93 g) se disolvieron en DMF (50 ml), y se añadió carbonato de cesio (4,82 g). Después de agitar a 50°C durante 6 h, la mezcla se dejó reposar durante una noche. Después de agitar a 50°C durante 4 horas adicionales, se añadieron un eq. adicional de carbonato de cesio y un eq. adicional del mesilato, y la mezcla se agitó a 50°C durante 4 h adicionales y se dejó reposar durante una noche. Después, la mezcla se agitó a 50°C durante 8 h adicionales y se dejó reposar durante 6 días, y luego se añadieron 0,5 eq. adicionales de carbonato de cesio y mesilato. Después de agitar a 50°C durante 8 h adicionales, la mezcla se dejó reposar durante 5 días, después se separó la DMF y el residuo se recogió con DCM/agua. La fase en DCM se separó y se concentró. El residuo se purificó utilizando gel de sílice (cartucho de 120 g, gradiente de 0-50% de n-heptano/MTB-éter en 60 min). Se obtuvieron 2,05 g del compuesto del título.

Tr de LC-MS: 1,72 min $[M+H-HOCH_3]^+$: 279,1 (met. a)

O5.075

3-Amino-N-metoxi-N-metil-5-pentafluorosulfanil-benzamida

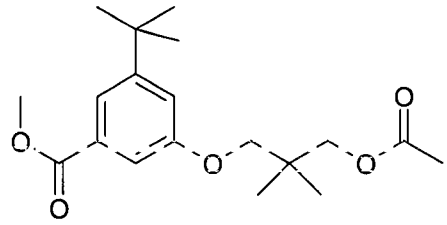


N-Metoxi-N-metil-5-nitro-3-pentafluorosulfanilbenzamida (O6.075; 4,2 g) se disolvió en metanol (120 ml), y se añadió níquel Raney (aproximadamente 700 mg). Con un globo de hidrógeno fijado, la hidrogenación se efectuó en un agitador magnético. Después de 5 h, el catalizador se separó mediante filtración y se lavó con metanol. El filtrado se concentró a presión reducida y el residuo se purificó mediante cromatografía preparativa. Las fracciones que contenían producto se combinaron, se liberaron del acetonitrilo, se basificaron con solución de hidrógeno-carbonato de sodio y se extrajeron tres veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. Se obtuvieron 1,73 g del compuesto deseado.

Tr de LC-MS: 1,27 min $[M+H]^+$: 307,0 (met. a)

O5.086

3-(3-Acetoxi-2,2-dimetilpropoxi)-5-terc-butilbenzoato de metilo

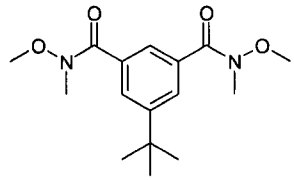


3-terc-Butil-5-hidroxibenzoato de metilo (O6.043; 1,79 g) se hizo reaccionar con acetato de 3-bromo-2,2-dimetilpropilo, se trató y se purificó de forma análoga a O2.85. Se obtuvieron 1,01 g del compuesto del título.

Tr de LC-MS: 2,01 min [M+H]$^+$: 337,1 (met. a)

O5.106

5-terc-Butil-N,N'-dimetoxi-N,N'-dimetilisoftalamida

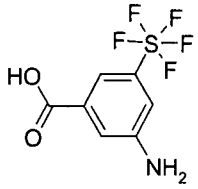


En un matraz de tres bocas de 4 l con condensador de reflujo y agitador mecánico, se añadió ácido 5-*terc*-butilisoftálico (300 g, 1,35 mol) a cloruro de tionilo (1,60 l, 2,62 kg, 22,0 mol). La suspensión resultante se agitó a 80°C. Después de 4 h, se había formado una solución transparente y el disolvente se separó mediante destilación. El residuo se secó luego a presión reducida y después se suspendió en diclorometano (1,5 l). Esta suspensión se enfrió hasta 0°C y se añadió hidrocloruro de *N,O*-dimetilhidroxilamina (395 g, 4,05 mol). Subsiguientemente, se añadió lentamente gota a gota trietilamina (1,50 l, 1,09 kg, 10,8 mol), de modo que la temperatura no excedía de 15°C. Una vez de haber agitado la mezcla a TA durante 16 h, se añadió agua (1 l). Las fases se separaron y la fase orgánica se lavó con solución saturada de NH_4Cl (2 × 500 ml), solución saturada de $NaHCO_3$ (2 × 500 ml) y solución saturada de NaCl (1 × 500 ml). La fase orgánica se secó ($MgSO_4$) y el disolvente se separó a presión reducida. El producto se obtuvo en forma de un sólido blanco (405 g).

Tr de LC-MS: 1,22 min [M+H]$^+$: 309 (met. a)

O6.007

Ácido 3-amino-5-pentafluorosulfanil-benzoico



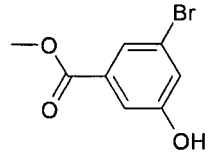
Ácido 3-pentafluorosulfanilbenzoico (15 g) se disolvió en ácido nítrico fumante (120 ml) y se agitó a TA con la exclusión de la humedad. Luego se añadió ácido sulfúrico concentrado (7,5 ml) y la mezcla se agitó a 75°C. Después de agitar a 75°C durante 8 h, la mezcla se dejó reposar durante una noche, después se añadió ácido sulfúrico adicional (1,5 ml) y la mezcla se calentó hasta 75°C mientras se agitaba durante 8 h. Después de dejar reposar durante una noche, Después de dejar reposar durante una noche, la mezcla se añadió a hielo-agua y se agitó durante 2 h. Después, el filtrado se separó mediante filtración con succión y se secó en alto vacío. Se obtuvieron 13,7 g de ácido 3-pentafluorosulfanil-5-nitrobenzoico.

Subsiguientemente, el ácido 3-pentafluorosulfanil-5-nitrobenzoico (5 g) se disolvió en metanol (300 ml), se añadió níquel Raney (aproximadamente 750 mg) y la hidrogenación se efectuó bajo una atmósfera de hidrógeno (globo de hidrógeno). Después de 3 h, el catalizador se separó mediante filtración y el residuo del filtro se lavó a fondo con metanol. El filtrado se concentró y se secó. El residuo se purificó utilizando gel de sílice (cartucho de 2 x 50 g, gradiente de 0-100% de n-heptano/EA en 60 min). Se obtuvieron 3,9 g del compuesto del título.

^{1}H RMN (400 MHz, DMSO-d_6) [ppm]: 13,30 (1 H); 7,37 (2 H); 7,23 (1 H); 5,98 (2 H)

O6.032

3-Bromo-5-hidroxibenzoato de metilo

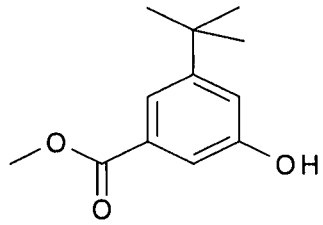


Ácido 3-bromo-5-hidroxibenzoico (3 g) se convirtió en el compuesto del título de forma análoga a O6.043. Se obtuvieron 2,52 g.

^{1}H RMN (500 MHz, DMSO-d_6) [ppm]: 10,40 (1 H); 7,47 (1 H); 7,33 (1 H); 7,22 (1 H); 3,84 (3 H)

O6.043

3-terc-Butil-5-hidroxibenzoato de metilo

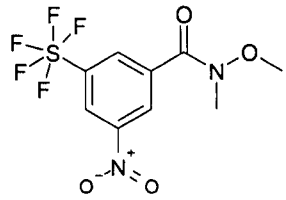


Se disolvió ácido 3-terc-butil-5-hidroxibenzoico (O7.043; 1,93 g) en metanol (20 ml) y se añadió lentamente gota a gota cloruro de tionilo (0,937 ml) mientras se agitaba. Después de agitar a 65°Cdurante 1 h, la mezcla se secó, el residuo se recogió en DCM, y la solución se lavó con una solución saturada de hidrógeno-carbonato sódico, se secó sobre MgSO4, se filtró y se concentró por evaporación rotatoria. Se obtuvieron 2,19 g del compuesto del título.

Tr de LC-MS: 1,44 min [M+H$^+$]: 209,2 (met. a)

O6.075

N-Metoxi-N-metil-5-nitro-3-pentafluorosulfanil-benzamida



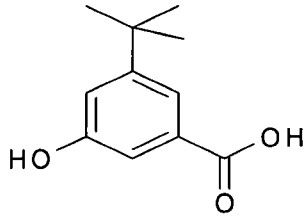
Ácido 3-pentafluorosulfanilbenzoico (5,0 g) se disolvió en ácido nítrico fumante (20 ml) y se agitó a TA con la exclusión de la humedad. Luego se añadió ácido sulfúrico concentrado (3 ml) y la mezcla se agitó a 75°C. Después de agitar a 75°C durante 5 h, se añadió ácido sulfúrico adicional (2 ml) y la mezcla se agitó a 75°C durante otras 2 h. Después de dejar reposar durante una noche, la mezcla se vertió en hielo-agua y se agitó durante 2 h. Después, el precipitado se separó mediante filtración con succión y se secó en alto vacío. Se obtuvieron 4,2 g de ácido 3-pentafluorosulfanil-5-nitrobenzoico. Se obtuvieron 900 mg adicionales a partir de las aguas madre después de extraer tres veces con cloruro de metileno, secar las fases en cloruro de metileno combinadas sobre sulfato de magnesio y concentrar el disolvente. Subsiguientemente, 4,0 g del ácido 3-pentafluorosulfanil-5-nitrobenzoico se disolvieron en cloruro de tionilo (25 ml) mientras se agitaba y se mantuvo a reflujo con la exclusión de la humedad durante 10 h. Después de reposar durante una noche a TA, se separó el cloruro de tionilo en exceso a presión reducida, y el residuo obtenido se disolvió en diclorometano (50 ml) y se mezcló mientras se agitaba con N,O-dimetilhidroxilamina × HCl (1,25 g) y dietilisopropilamina (1,66 g).

Después de agitar a TA durante 1 h, la mezcla se concentró a presión reducida, y el residuo se disolvió en acetato de etilo y se lavó cinco veces con agua. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. Los 4,2 g de producto bruto obtenidos se utilizaron directamente en la etapa siguiente.

Tr de LC-MS: 1,50 min [M+H$^+$]: 337,0 (met. a)

O7.043

Ácido 3-terc-butil-5-hidroxibenzoico

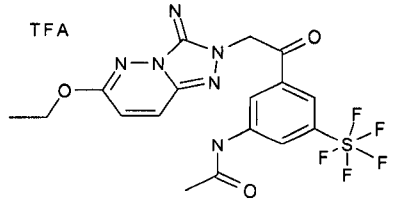


Se disolvió ácido 3-bromo-5-terc-butilbenzoico (5 g) en THF (180 ml), se añadió gota a gota n-butillitio (18,7 ml, 2,5 M en hexano) en una atmósfera de argón y a -75°C y se agitó durante 30 min más. Después, se añadió gota a gota borato de trimetilo (6,63 ml) y se dejó que la mezcla volviera a la TA durante 1 h. Después, se añadieron sucesivamente hidróxido sódico (0,778 g), disuelto en 2 ml de agua, y peróxido de hidrógeno (12,89 ml, al 30%). Después de agitar a TA durante 3 h, la mezcla se dejó en reposo durante el fin de semana. Después, se añadieron agua y EA, la mezcla se ajustó a un valor de pH de 3 con ácido clorhídrico 1 N y la fase de EA se retiró. Esta fase se lavó tres veces con agua, se secó, se filtró y se concentró. El residuo se purificó usando gel de sílice (cartucho de 120 g, gradiente de 0-50% de n-heptano/MtB éter en 60 min). Se obtuvieron 1,94 g del compuesto del título.

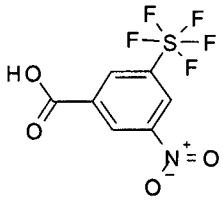
Tr de LC-MS: 1,18 min [M+H$^+$]: 195,1 (met. a)

Ejemplo 1

N-[3-[2-(6-Etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)acetil]-5-(pentafluorosulfanil)fenil]acetamida en forma de la sal del ácido trifluoroacético



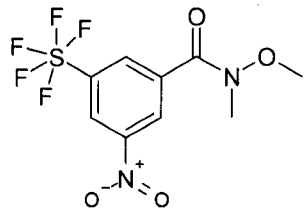
a) Ácido 3-nitro-5-pentafluorosulfanilbenzoico



Se disolvió ácido 3-pentafluorosulfanilbenzoico (5,0 g) en ácido nítrico fumante (20 ml) y se agitó a TA con exclusión de humedad. Después, se añadió ácido sulfúrico concentrado (3 ml) y la mezcla se agitó a 75°C. Después de agitar a 75°C durante 5 h, se añadió más cantidad de ácido sulfúrico (1,5 ml) y, después de agitar a 75°C durante 2 h, se dejó en reposo durante una noche. Después, la mezcla se añadió a hielo-agua y se agitó durante 2 h. El precipitado formado se retiró por filtración con succión y se secó a alto vacío. Se obtuvieron 4,2 g de ácido 3-pentafluorosulfanil-5-nitrobenzoico. Se obtuvieron 900 mg más a partir de las aguas madre después de la extracción tres veces con cloruro de metileno, el secado de las fases de cloruro de metileno combinadas sobre sulfato de magnesio y la concentración del disolvente. El precipitado se usó en la siguiente etapa sin purificación adicional.

^{1}H RMN (400 MHz, DMSO-d_6) [ppm]: 8,32 (1 H); 8,80 (1 H); 8,62 (1 H)

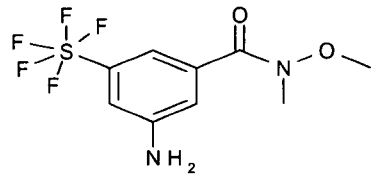
b) N-Metoxi-N-metil-5-nitro-3-pentafluorosulfanilbenzamida



Se disolvió ácido 3-nitro-5-pentafluorosulfanilbenzoico (4,0 g) en cloruro de tionilo (25 ml) mientras se agitaba y se mantuvo a la temperatura de reflujo con exclusión de la humedad durante 10 h. Después de dejar en reposo durante una noche, el exceso de cloruro de tionilo se retiró a presión reducida a TA y el residuo resultante se disolvió en diclorometano (50 ml) y se mezcló con hidrocloruro de N,O-dimetilhidroxilamina (1,25 g) y dietilisopropilamina (1,66 g) mientras se agitaba. Después de agitar a TA durante 1 h, la mezcla se concentró a presión reducida y el residuo se disolvió en acetato de etilo y se lavó 5 veces con agua. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El producto en bruto resultante (4,2 g) se usó directamente en la siguiente etapa.

Tr de LC-MS: 1,50 min [M+H$^+$]: 337,0 (met. a)

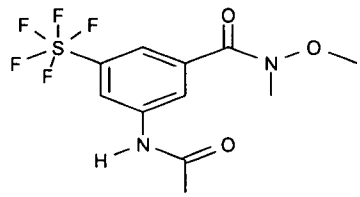
c) 3-Amino-N-metoxi-N-metil-5-pentafluorosulfanilbenzamida



Se disolvió N-metoxi-N-metil-5-nitro-3-pentafluorosulfanilbenzamida (4,2 g) en metanol (120 ml) y se añadió níquel Raney (aprox. 700 mg). Con un globo de hidrógeno unido, se realizó la hidrogenación en un agitador magnético. Después de 5 h, el catalizador se retiró por filtración y se lavó con metanol. El filtrado se concentró a presión reducida y el residuo se purificó por medio de cromatografía preparativa. Las fracciones que contenían el producto se combinaron, se liberaron del acetonitrilo, se basificaron con una solución de hidrogenocarbonato sódico y se extrajeron tres veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. Se obtuvieron 1,73 g del compuesto del título.

Tr de LC-MS: 1,27 min [M+H$^+$]: 307,0 (met. a)

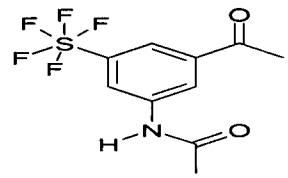
d) 3-Acetilamino-N-metoxi-N-metil-5-(pentafluorosulfanil)benzamida



Se disolvió 3-amino-N-metoxi-N-metil-5-pentafluorosulfanilbenzamida (1,2 g) en cloruro de metileno (15 ml) y se añadió trietilamina (0,7 ml) seguido de anhídrido acético (1,75 ml) mientras se agitaba con exclusión de la humedad. Después de agitar a TA durante 3 h, se añadieron agua y una solución saturada de hidrogenocarbonato sódico, se separaron las fases y la fase de cloruro de metileno se lavó tres veces más con agua, se secó sobre sulfato magnésico, se filtró y se concentró. El producto resultante (1,3 g) se usó en la siguiente etapa sin purificación adicional.

Tr de LC-MS: 1,26 min [M+H$^+$]: 349,0 (met. a)

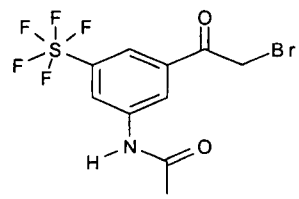
e) N-[3-Acetil-5-(pentafluorosulfanil)fenil]acetamida



Se disolvió 3-acetilamino-N-metoxi-N-metil-5-(pentafluorosulfanil)benzamida (1,2 g) en THF absoluto (30 ml) y se agitó a 0°C con hexametildisilazida de litio (7,1 µl; densidad: 0,8 g/l; 23% en *terc*-butil metil éter) durante 30 min. Después, a 0°C, se añadió lentamente gota a gota bromuro de metilmagnesio (2,87 ml, 3 M en éter dietílico) mientras se agitaba. Después de agitar a TA durante 2,5 h, se añadió más cantidad de bromuro de metilmagnesio (1 ml, 3 M en éter dietílico) y la mezcla se agitó de nuevo durante 2,5 h. Para el tratamiento, se añadió gota a gota ácido clorhídrico 1 N mientras se enfriaba con hielo, seguido de agua y acetato de etilo. La fase orgánica se retiró y la fase de agua se extrajo dos veces más con acetato de etilo. Las fases combinadas de acetato de etilo se secaron sobre sulfato sódico, se filtraron y se concentraron. El producto en bruto (1,03 g) se combinó con un producto en bruto preparado de la misma manera (75 mg) y se purificó usando gel de sílice con diclorometano-metanol como eluyente. Se obtuvieron 860 mg del compuesto deseado.

Tr de LC-MS: 1,54 min [M+H$^+$]: 304,0 (met. a)

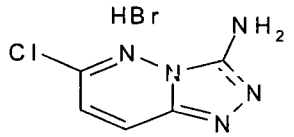
f) N-[3-(2-Bromoacetil)-5-(pentafluorosulfanil)fenil]acetamida (O1.001)

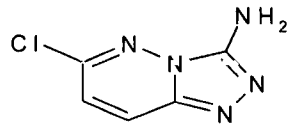


Se disolvió N-[3-acetil-5-(pentafluorosulfanil)fenil]acetamida (859 mg) en una mezcla de metanol (10 ml) y THF (10 ml) y se añadió en porciones tribromuro de feniltrimetilamonio (1,065 g) mientras se agitaba. Después de agitar a TA durante 2 h, la mezcla se calentó a 40°Cdurante 3 h más. Después de un periodo de refrigeración, la mezcla de reacción se añadió a ácido sulfúrico 2 N y la fase acuosa se extrajo 3 veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron. El producto en bruto se purificó usando gel de sílice con acetato de etilo/heptano como eluyente. Se obtuvieron 480 mg del compuesto deseado.

Tr de LC-MS: 1,47 min [M+H$^+$]: 382,0 (met. a)

g) 6-Cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina en forma del hidrobromuro (W2.001) y 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001a)





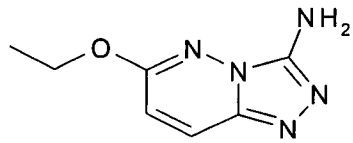
Se disolvió (6-cloropiridazin-3-il)hidrazina (1 g) en una mezcla de etanol (22,5 ml) y agua (9 ml) a TA mientras se agitaba. Después, se añadió gota a gota bromuro de cianógeno (2,8 ml, 5 M en acetonitrilo) mientras se agitaba. Después de agitar durante 6 h y dejar en reposo durante una noche, el precipitado se retiró por filtración con succión y se secó. De esta manera, se obtuvieron 1,14 g del producto deseado en forma del hidrobromuro.

Tr de LC-MS: 0,24 min [M+H$^+$]: 170,1 (met. a)

Se obtuvo más cantidad de producto en forma de la base libre, por basificación de las aguas madre con una solución saturada de carbonato potásico. El precipitado formado se retiró por filtración con succión y se secó (326 mg).

Tr de LC-MS: 0,24 min [M+H$^+$]: 170,1 (met. a)

h) 6-Etoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina



Se recogió hidrobromuro de 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001; 1,1 g) en una gran cantidad de agua y la mezcla se hizo alcalina con una solución saturada de carbonato potásico. El sólido que precipitó se retiró por filtración con succión y se secó (388 mg). La extracción repetida de las aguas madre con diclorometano, el secado de las fases orgánicas combinadas sobre sulfato sódico, la filtración y la concentración produjeron 228 mg más de producto en total. La base libre resultante (616 mg) se disolvió en etanol absoluto (40 ml) y se mezcló en porciones con etóxido sódico sólido (990 mg). Después de agitar a 55°C durante 2 h, se añadió agua y la fase acuosa se extrajo tres veces con diclorometano. Los extractos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron. Se obtuvieron 709 mg del compuesto deseado.

Tr de LC-MS: 0,51 min [M+H$^+$]: 180,1 (met. a)

i) N-[3-[2-(6-Etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)acetil]-5-

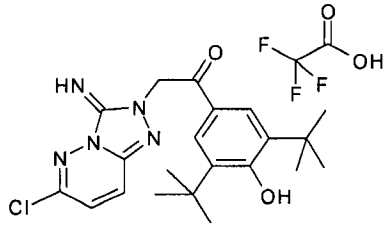
(pentafluorosulfanil)fenil]acetamida en forma de la sal del ácido trifluoroacético

Se cargó inicialmente 6-etoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W1.001; 40 mg) en DMF absoluta (3,5 ml) mientras se agitaba y se añadió gota a gota N-[3-(2-bromoacetil)-5-(pentafluorosulfanil)fenil]acetamida (O1.001; 94 mg), disuelta en DMF absoluta (1,5 ml). Después de agitar a TA durante 5 h y dejar en reposo durante una noche, el disolvente se retiró y el residuo se purificó por medio de cromatografía preparativa (met. A). Las fracciones que contenían el producto se combinaron, se liberaron del acetonitrilo y se liofilizaron (90 mg). Para retirar el isómero catiónico, se realizó una purificación adicional usando gel de sílice con un gradiente de diclorometano/metanol. Las fracciones del producto deseado, que eluye primero, se combinaron y se secaron. Después, el residuo se purificó adicionalmente por medio de cromatografía preparativa (met. A). Las fracciones que contenían el producto se combinaron, se liberaron del acetonitrilo y se liofilizaron. Se obtuvieron 42 mg del compuesto deseado.

Tr de LC-MS: 1,12 min [M+H$^+$]: 481,0 (met. a)

Ejemplo 2

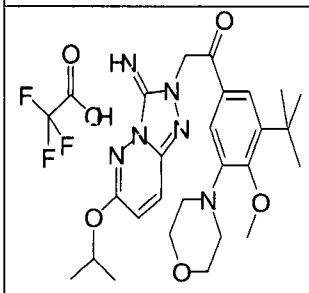
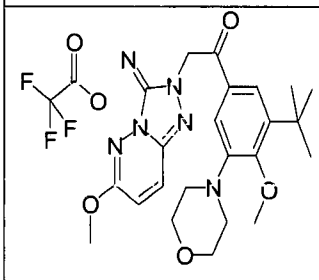
2-(6-Cloro-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(3,5-di-terc-butil-4-hidroxifenil)etanona



Se cargó inicialmente 6-cloro-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W2.001a; 30 mg) en DMF (3,5 ml) a TA mientras se agitaba y se añadió gota a gota 2-bromo-1-(3,5-di-terc-butil-4-hidroxifenil)etanona (O1.002; 58 mg) disuelta previamente en DMF (0,5 ml). La mezcla de reacción se agitó a TA durante 30 min y después se calentó a 60°C durante 5 h. Después de dejar en reposo durante una noche, el disolvente se retiró a presión reducida y el residuo se purificó por medio de HPLC preparativa (met. A). Las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida y se liofilizaron. Se obtuvieron 29 mg del compuesto del título.

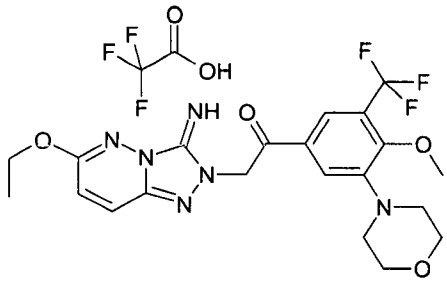
Tr de LC-MS: 1,28 min [M+H$^+$]: 416,1 (met. a)

Los siguientes se obtuvieron de forma análoga al ejemplo 2:

Ej. 3	Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-isopropoxi-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona (16 mg)					
		W 1.003 15 mg	O 1.003 29 mg	Tr de LC-MS [min] 1,35	[M+H+] 483,3 (met. a)	
Ej. 4	Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-metoxi-[1,2,4] triazolo[4,3-b]piridazin-2-il)etanona (34 mg)					
		W 1.002 30 mg	O 1.003 74 mg	Tr de LC-MS [min] 1,24	[M+H+] 455,1 (met. a)	

Ejemplo 5

Sal del ácido trifluoroacético de 2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(4-metoxi-3-morfolin-4-il-5-trifluormetilfenil)etanona

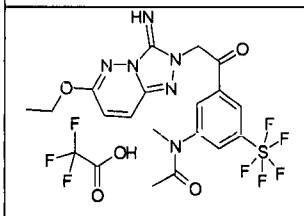
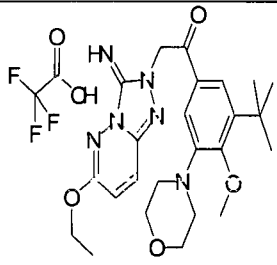
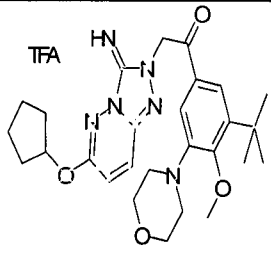


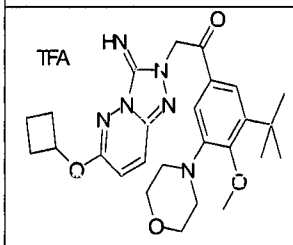
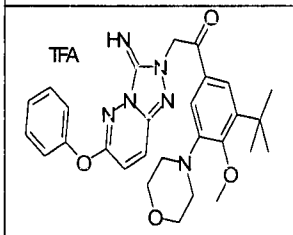
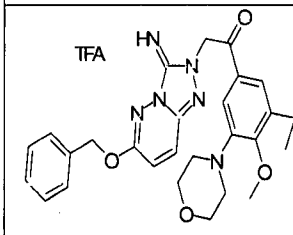
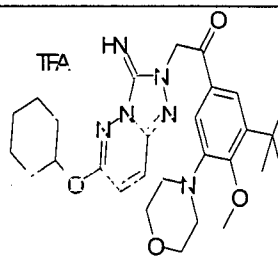
Se cargó inicialmente 6-etoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W1.001; 10 mg) en DMF (3,5 ml) a TA mientras se agitaba y se añadió gota a gota 2-bromo-1-(4-metoxi-3-morfolin-4-il-5-trifluorometilfenil)etanona (O1.004; 21 mg) disuelta previamente en DMF (1,5 ml). La mezcla de reacción se agitó a TA durante 2 h. Después de dejar en reposo durante una noche, el disolvente se retiró a presión reducida y el residuo se purificó por medio de HPLC preparativa (met. A). Las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a

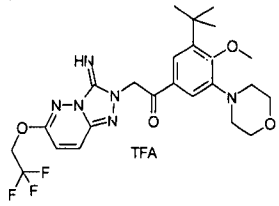
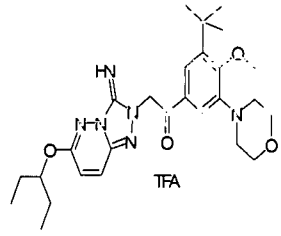
presión reducida y se liofilizaron. El compuesto del título contaminado con el producto de la sustitución 1 se purificó usando gel de sílice con un gradiente de diclorometano/metanol. Las fracciones limpias del producto se secaron, se recogieron con un poco de acetonitrilo/agua+TFA al 0,05% y se liofilizaron. Se obtuvieron 7 mg del compuesto del título.

Tr de LC-MS: 1,20 min [M+H$^+$]: 481,1 (met. a)

Los siguientes se obtuvieron de forma análoga a los ejemplos anteriores:

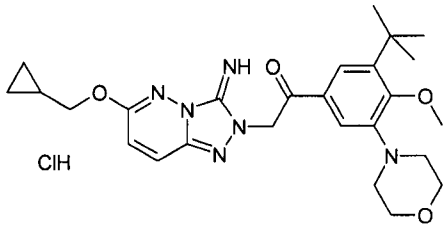
<table>
<tr><td>Ej. 6</td><td colspan="6">Sal del ácido trifluoroacético de N-[3-[2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)acetil]-5-(penta-fluorosulfanil)fenil]-N-metilacetamida (6 mg)</td></tr>
<tr><td></td><td>  </td><td>W
1.001
15 mg</td><td>O
1.005
29 mg</td><td>Tr de LC-MS [min]
1,10</td><td>[M+H$^+$]
495,0
(met. a)</td><td>análogo al ej. 5</td></tr>
<tr><td>Ej. 7</td><td colspan="6">Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona (15 mg)</td></tr>
<tr><td></td><td>  </td><td>W
1.001
30 mg</td><td>O
1.003
62 mg</td><td>Tr de LC-MS [min]
1,34</td><td>[M+H$^+$]
469,2
(met. a)</td><td>análogo al ej. 2</td></tr>
<tr><td>Ej. 8</td><td colspan="6">Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclopentiloxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona (4 mg)</td></tr>
<tr><td></td><td>  </td><td>W
1.007
15 mg</td><td>O
1.003
18 mg</td><td>Tr de LC-MS [min]
1,44</td><td>[M+H$^+$]
509,2
(met. a)</td><td>análogo al ej. 5, pero en presencia de 7,3 µl de TEA</td></tr>
</table>

Ej. 9	Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclobutoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona (41 mg)					
		W 1.004 15 mg	O 1.003 16 mg	Tr de LC-MS [min] 1,40	[M+H⁺] 495,2 (met. a)	análogo al ej. 5
Ej. 10	Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-fenoxi-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona (29 mg)					
		W 1,013 18 mg	W 1.003 32 mg	Tr de LC-MS [min] 1,35	[M+H⁺] 517,3 (met. a)	análogo al ej. 5
Ej. 11	Sal del ácido trifluoroacético de 2-(6-benciloxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)etanona (27 mg)					
		W 1.005 20 mg	O 1.003 34 mg	Tr de LC-MS [min] 1,40	[M+H⁺] 531,2 (met. a)	análogo al ej. 5
Ej. 12	Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclohexiloxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona (5 mg)					
		W 1.006 20 mg	O 1.003 18 mg	Tr de LC-MS [min] 1,54	[M+H⁺] 523,3 (met. a)	análogo al ej. 5, pero en presencia de 7,2 µl de TEA
Ej. 13	Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[3-imino-6-(2,2,2-trifluoro-etoxi)-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (25 mg)					

		W 1.014 23 mg	O 1.003 39 mg	Tr de LC-MS [min] 1,33	[M+H$^+$] 523,2 (met. a)	análogo al ej. 5
Ej. 14	Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (14 mg)					
		W 1.008 20 mg	O 1.003 37 mg	Tr de LC-MS [min] 1,48	[M+H$^+$] 511,2 (met. a)	análogo al ej. 5

Ejemplo 15

Hidrocloruro de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclopropilmetoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona

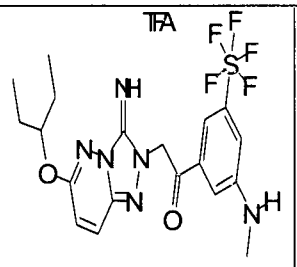
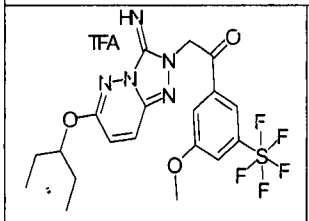


Se cargó inicialmente 6-ciclopropilmetoxi-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W1.009; 350 mg) en DMF (5 ml) a TA mientras se agitaba y se añadió gota a gota 2-bromo-1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)etanona (O1.003; 631 mg) disuelta previamente en DMF (5 ml). La mezcla de reacción se agitó a TA durante 14 h. Después, el disolvente se retiró a presión reducida y el residuo se purificó usando gel de sílice (cartucho de 40 g, diclorometano/etanol gradiente de 0-40% en 60 min). El producto se recogió con un poco de acetonitrilo, se diluyó con agua y, después de la adición de 2 equiv. de HCl, se liofilizó. Se obtuvieron 500 mg del compuesto del título.

Tr de LC-MS: 1,37 min [M+H$^+$]$^+$: 495,2 (met. a)

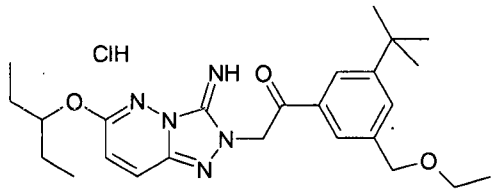
Los siguientes se obtuvieron de forma análoga a los ejemplos anteriores:

Ej. 16	Sal del ácido trifluoroacético de 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metilamino-5-(pentafluorosulfanil)fenil]etanona (11 mg)

		W 1.008 19 mg	O 1.006 30 mg	Tr de LC-MS [min] 1,35	[M+H+] 495,1 (met. a)	análogo al ej. 5
Ej. 17	Sal del ácido trifluoroacético de 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona (23 mg)					
		W 1.008 25 mg	O 1.007 40 mg	Tr de LC-MS [min] 1,35	[M+H+] 496,1 (met. a)	análogo al ej. 5

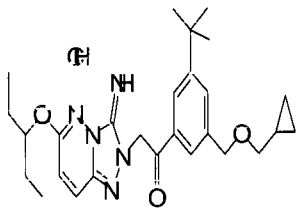
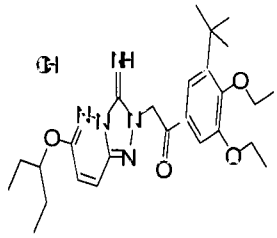
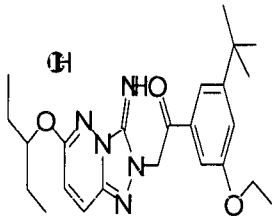
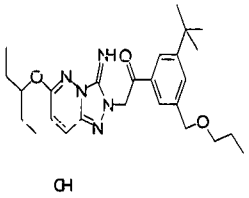
Ejemplo 18

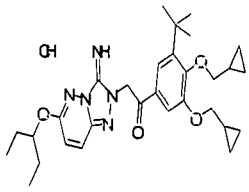
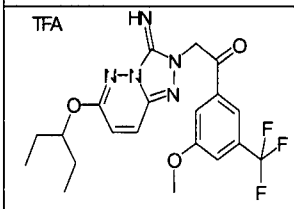
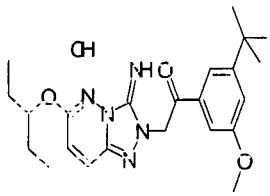
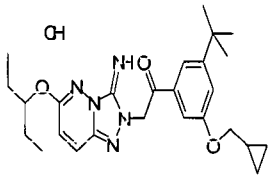
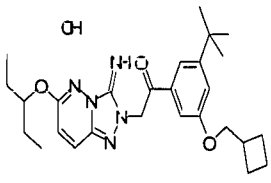
Hidrocloruro de 1-(3-terc-butil-5-etoximetilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona

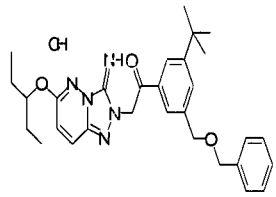
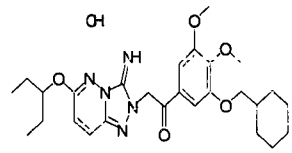
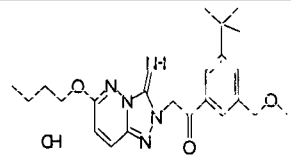
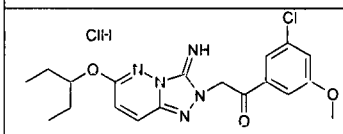
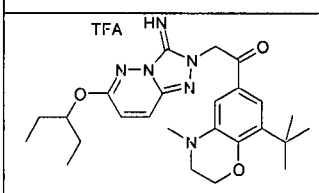


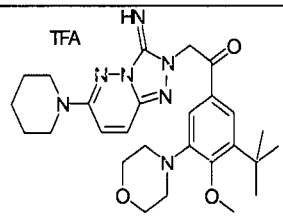
Se cargó inicialmente 6-(1-etilpropoxi)-[1,2,4]triazolo[4,3-b]piridazin-3-ilamina (W1.008; 205 mg) en DMF (5 ml) a TA mientras se agitaba y se añadió gota a gota 2-bromo-1-(3-terc-butil-5-etoximetilfenil)etanona (O1.003; 290 mg) disuelta previamente en DMF (5 ml). La mezcla de reacción se agitó a TA durante 14 h. Después, el disolvente se retiró a presión reducida y el residuo se purificó usando gel de sílice (cartucho de 40 g, diclorometano/etanol gradiente de 0-40% en 60 min). El producto aún contaminado se purificó posteriormente por medio de HPLC preparativa. Las fracciones limpias del producto se combinaron, se liberaron del acetonitrilo a presión reducida y se liofilizaron. El residuo se disolvió en agua y acetonitrilo y, después de la adición de 3 equiv. de HCl, se liofilizó. Se obtuvieron 72 mg del compuesto del título. Tr de LC-MS: 1,44 min [M+H+]: 454,5 (met. a)

Los siguientes se prepararon de forma análoga a los ejemplos anteriores:

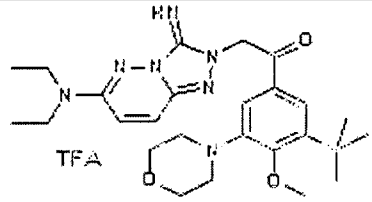
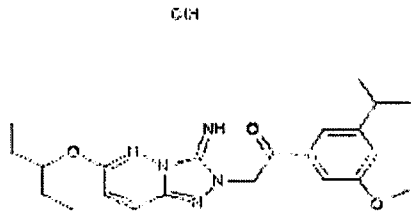
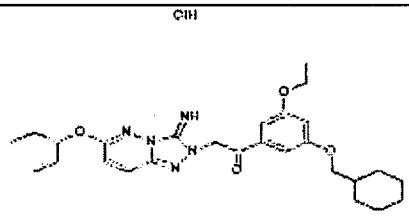
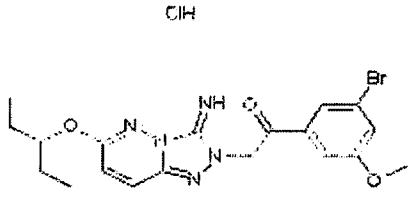
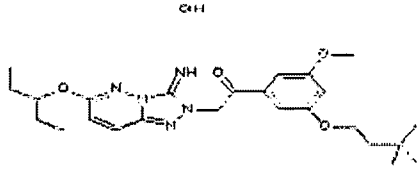
Ej. 19	Hidrocloruro de 1-(3-terc-butil-5-ciclopropilmetoximetilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (155 mg)					
		W 1.008 198 mg	O 1.009 304 mg	Tr de LC-MS [min] 3,36	[M+H$^+$] 480,2 (met. d)	análogo al ej. 18
Ej. 20	Hidrocloruro de 1-(3-terc-butil-4,5-dietoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (96 mg)					
		W 1.008 130 mg	O 1.010 202 mg	Tr de LC-MS [min] 3,47	[M+H$^+$] 484,1 (met. d)	análogo al ej. 18
Ej. 21	Hidrocloruro de 1-(3-terc-butil-5-etoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (114 mg)					
		W 1.008 140 mg	O 1,011 189 mg	Tr de LC-MS [min] 1,46	[M+H$^+$] 440,5 (met. a)	análogo al ej. 18
Ej. 22	Hidrocloruro de 1-(3-terc-butil-5-propoximetilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (92 mg)					
		W 1.008 180 mg	O 1.012 266 mg	Tr de LC-MS [min] 3,00	[M+H$^+$] 468,1 (met. d)	análogo al ej. 18
Ej. 23	Hidrocloruro de 1-(3-terc-butil-4,5-bis(ciclopropilmetoxi)fenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (112 mg)					

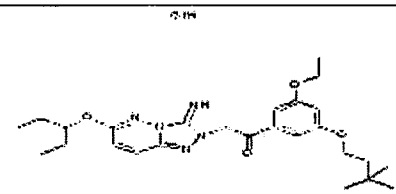
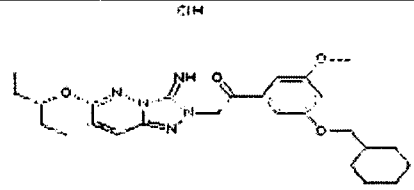
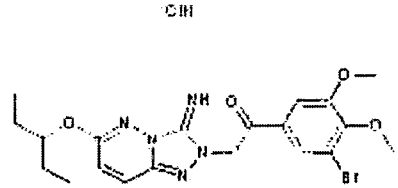
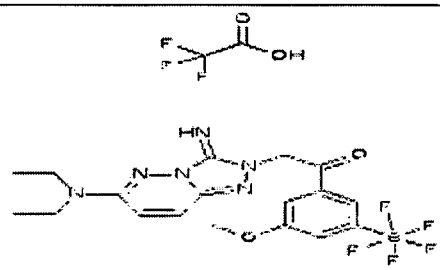
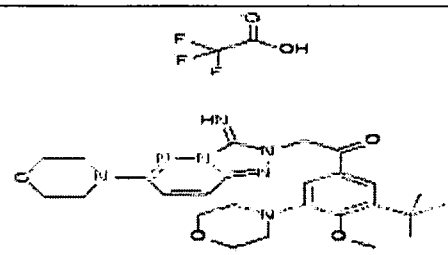
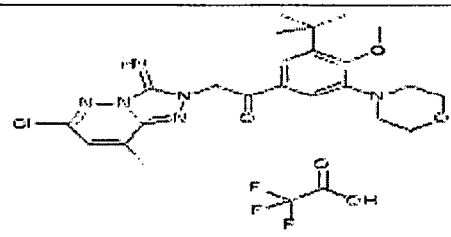
		W 1.008 165 mg	O 1.013 295 mg	Tr de LC-MS [min] 1,662	[M+H+] 536,5 (met. a)	análogo al ej. 18
Ej. 24	Sal del ácido trifluoroacético 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(3-metoxi-5-trifluorometilfenil)etanona (31 mg)					
		W 1.008 25 mg	O .,014 34 mg	Tr de LC-MS [min] 1,33	[M+H+] 438,1 (met. a)	análogo al ej. 2
Ej. 25	Hidrocloruro de 1-(3-terc-butil-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (176 mg)					
		W 1.008 200 mg	O 1.015 258 mg	Tr de LC-MS [min] 3,18	[M+H+] 426,1 (met. d)	análogo al ej. 18
Ej. 26	Hidrocloruro de 1-(3-terc-butil-5-ciclopropilmetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (152 mg)					
		W 1.008 180 mg	O 1.016 265 mg	Tr de LC-MS [min] 3,44	[M+H+] 466,3 (met. d)	análogo al ej. 18
Ej. 27	Hidrocloruro de 1-(3-terc-butil-5-ciclobutilmetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (137 mg)					
		W 1.008 180 mg	O 1.017 276 mg	Tr de LC-MS [min] 1,58	[M+H+] 480,5 (met. a)	análogo al ej. 18
Ej. 28	Hidrocloruro de 1-(3-benciloximetil-5-terc-butilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (183 mg)					

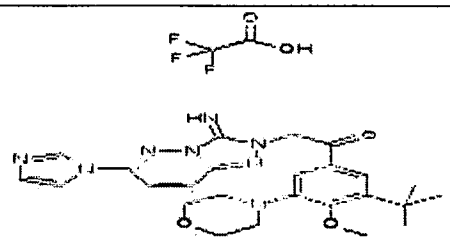
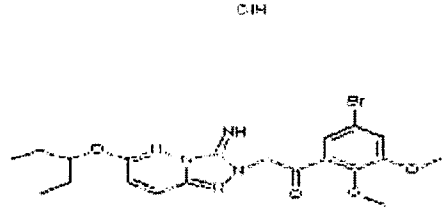
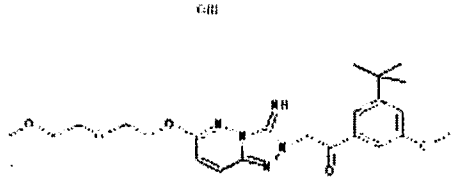
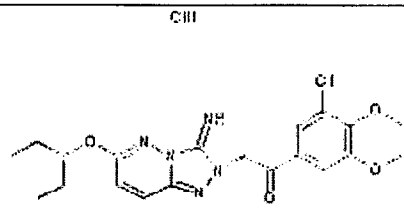
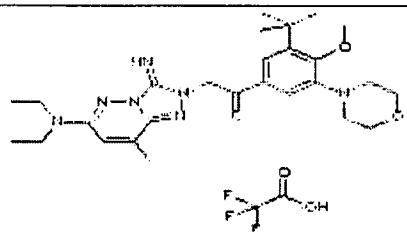
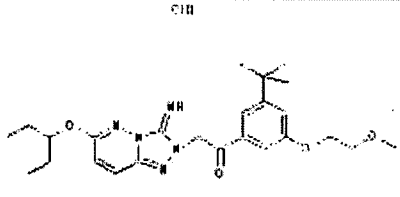
		W 1.008 200 mg	O 1.018 339 mg	Tr de LC-MS [min] 1,53	[M+H+] 516,5 (met. a)	análogo al ej. 18
Ej. 29	Hidrocloruro de 1-(3-ciclohexilmetoxi-4,5-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (76 mg)					
		W 1.008 75 mg	O 1.019 126 mg	Tr de LC-MS [min] 1,50	[M+H+] 512,5 (met. a).	análogo al ej. 18
Ej. 30	Hidrocloruro de 2-(6-butoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(3-terc-butil-5-metoximetilfenil)etanona (83 mg)					
		W 1.010 240 mg	O 1.020 347 mg	Tr de LC-MS [min] 1,33	[M+H+] 426,3 (met. a)	análogo al ej. 18
Ej. 31	Hidrocloruro de 1-(3-cloro-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (169 mg)					
		W 1.008 250 mg	O 1.021 298 mg	Tr de LC-MS [min] 1,28	[M+H+] 404,2 (met. a)	análogo al ej. 18
Ej. 32	Sal del ácido trifluoroacético de 1-(8-terc-butil-4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-6-il)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona (13 mg)					
		W 1.008 25 mg	O 1.022 37 mg	Tr de LC-MS [min] 1,43	[M+H+] 467,3 (met. a)	análogo al ej. 5
Ej. 33	Sal del ácido trifluoroacético de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-piperidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona (30 mg)					

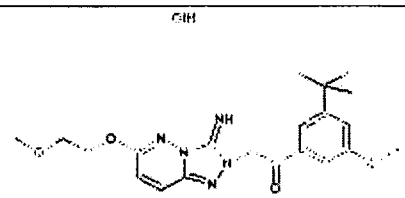
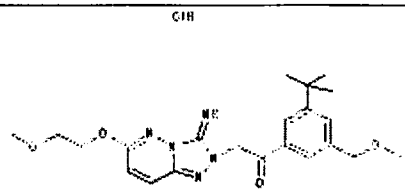
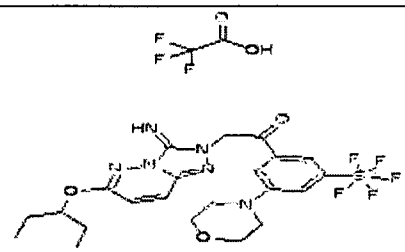
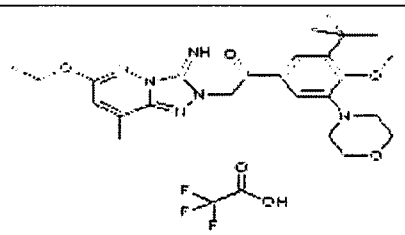
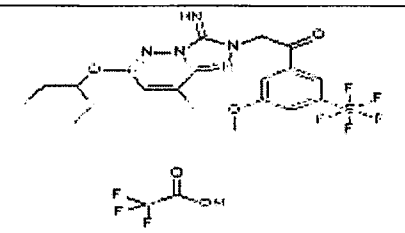
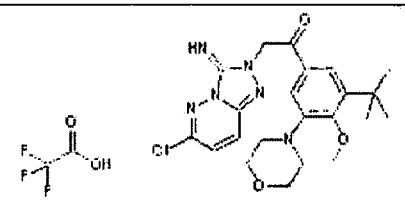
		W 1.020 25 mg	O 1.003 42 mg	Tr de LC-MS [min] 1,37	[M+H+] 508,3 (met. a)	análogo al ej. 5

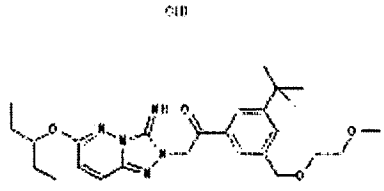
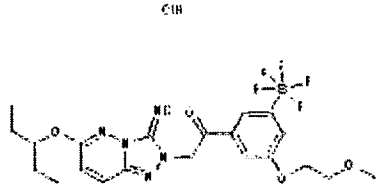
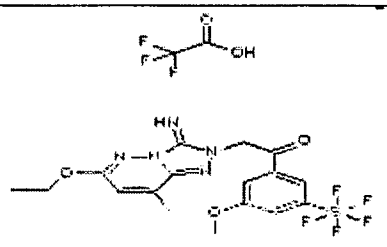
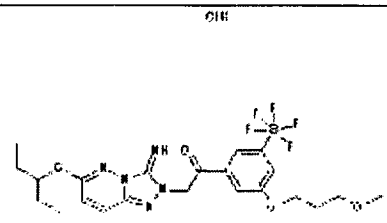
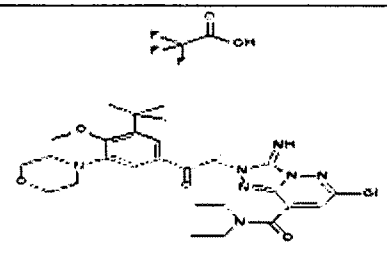
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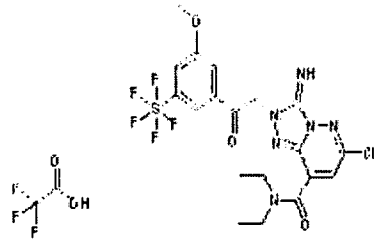
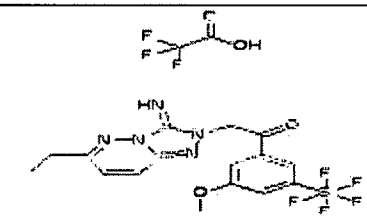
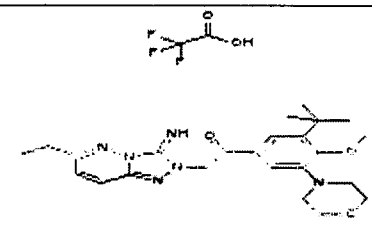
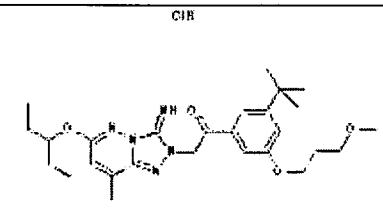
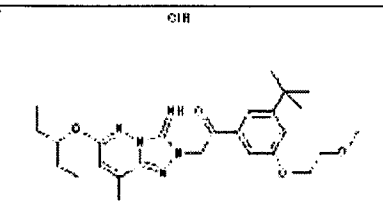
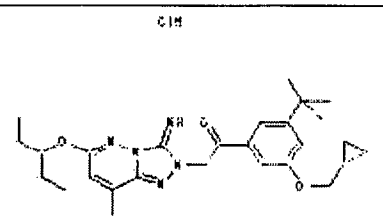
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 034		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-dietilamino-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,37	496,3 (met. a)
Ej.: 035		Hidrocloruro de 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(3-isopropil-5-metoxifenil)etanona	1,36	412,3 (met. a)
Ej.: 036		Hidrocloruro de 1-(3-ciclohexilmetoxi-5-etoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,56	496,4 (met. a)
Ej.: 037		Hidrocloruro de 1-(3-bromo-5-metoxi-fenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,3	448,1 (met. a)
Ej.: 038		Hidrocloruro de 1-[3-(3,3-dimetilbutoxi)-5-metoxifenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,52	470,4 (met. a)

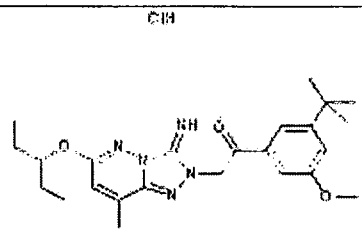
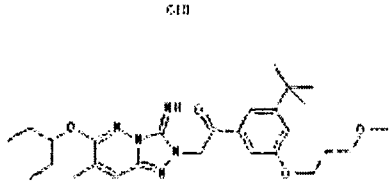
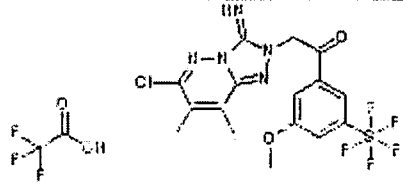
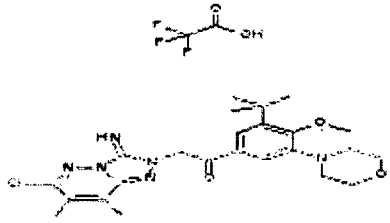
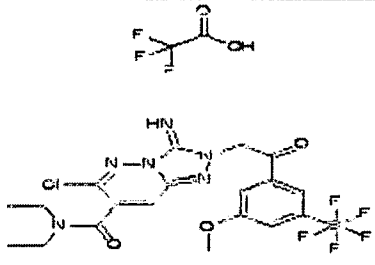
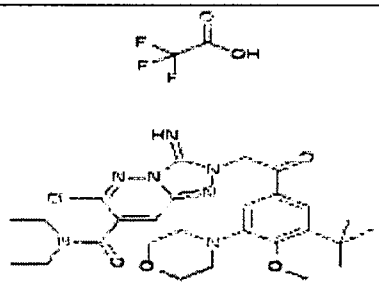
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 039		Hidrocloruro de 1-[3-(3,3-dimetilbutoxi)-5-etoxifenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,56	484,4 (met. a)
Ej.: 040		Hidrocloruro de 1-(3-ciclohexilmetoxi-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,55	482,4 (met. a)
Ej.: 041		Hidrocloruro de 1-(3-bromo-4,5-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona	1,29	478,1 (met. a)
Ej.: 042		Sal del ácido 2-(6-dietilamino-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluoro-sulfanil)fenil]etanona trifluoroacético	1,29	481,1 (met. a)
Ej.: 043		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-morfolin-4-il-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona trifluoroacético	1,24	510,2 (met. a)
Ej.: 044		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,27	478,1 (met. a)

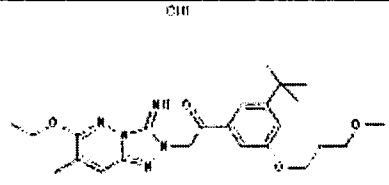
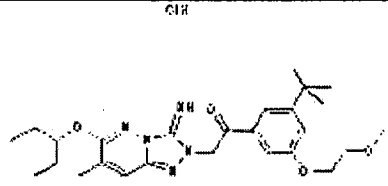
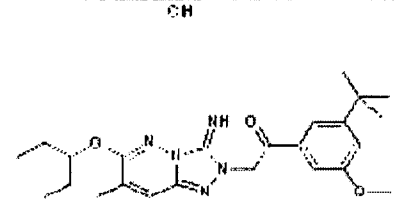
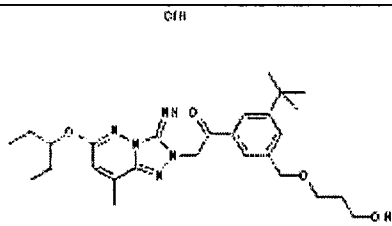
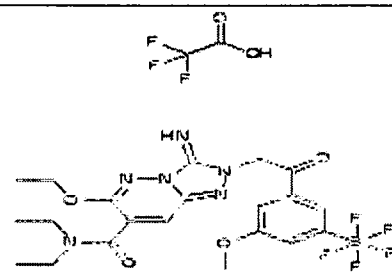
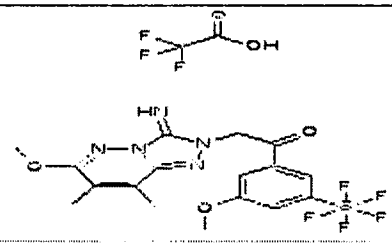
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 045		Sal de ácido trifluoroacético 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-imidazol-1-il-3-imino-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona	1,12	491,1 (met. a)
Ej.: 046		Hidrocloruro de 1-(5-bromo-2,3-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,35	479,1 (met. a)
Ej.: 047		Hidrocloruro de 1-(3-terc-butil-5-metoxi-fenil)-2-[3-imino-6-[2-(2-metoxietoxi)etoxi]-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona	1,22	458,3 (met. a)
Ej.: 048		1-(3-cloro-4,5-dimetoxi-fenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,3	434,1 (met. a)
Ej.: 049		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-dietilamino-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,42	510,4 (met. a)
Ej.: 050		Hidrocloruro de 1-[3-terc-butil-5-(2-metoxi-etoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,42	470,3 (met. a)

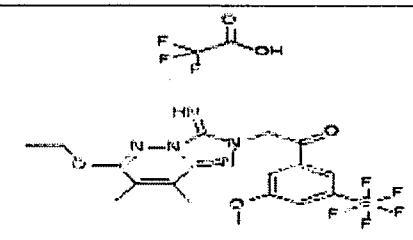
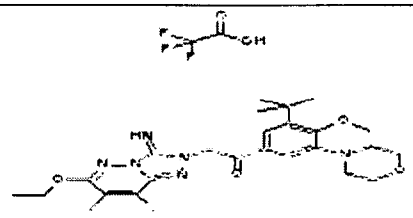
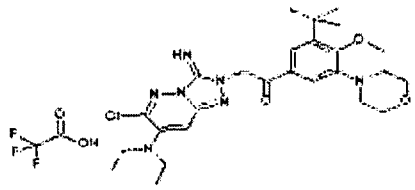
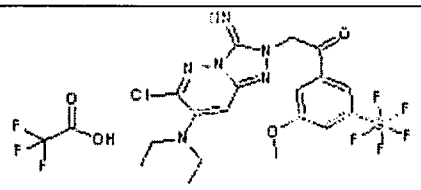
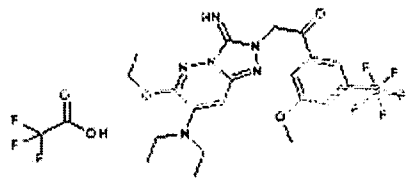
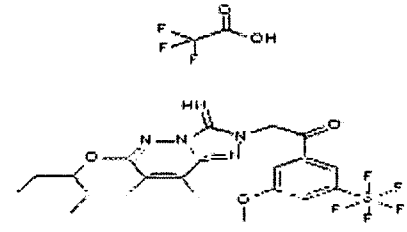
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 051		Hidrocloruro de 1-(3-terc-butil-5-metoxi-fenil)-2-[3-imino-6-(2-metoxietoxi)-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,21	414,2 (met. a)
Ej.: 052		Hidrocloruro de 1-(3-terc-butil-5-metoxi-metilfenil)-2-[3-imino-6-(2-metoxietoxi)-[1,2,4]triazolo[4,3-]piridazin-2-il]etanona	1,21	428,3 (met. a)
Ej.: 053		Sal del ácido 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-morfolin-4-il-5-(pentafluorosulfanil)fenil]-etanona trifluoroacético	1,34	551,2 (met. a)
Ej.: 054		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,35	483,3 (met. a)
Ej.: 055		Sal del ácido 2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metoxi-5-(pentafluoro-sulfanil)fenil]etanona trifluoroacético	1,41	510,1 (met. a)
Ej.: 056		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-3-imino-[1,2,4]triazolo-[4,3-b]piridazin-2-il)-etanona trifluoroacético	1,23	459,1 (met. a)

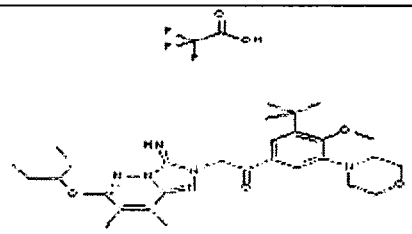
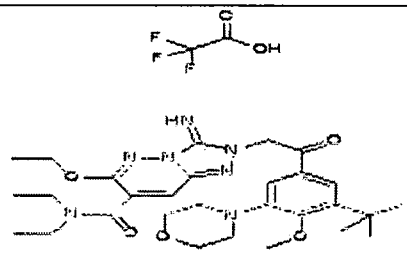
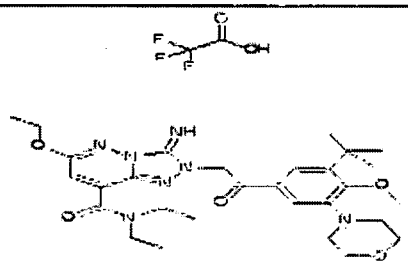
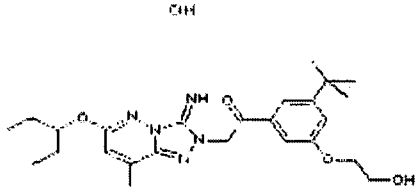
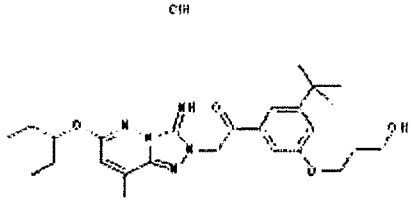
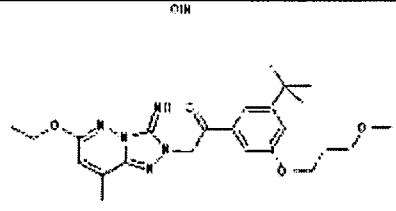
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 057		Hidrocloruro de 1-[3-terc-butil-5-(2-metoxi-metoximetil)fenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,38	484,4 (met. a)
Ej.: 058		Hidrocloruro de 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-(2-metoxietoxi)-5-(pentafluorosulfanil)-fenil]etanona	1,38	484,4 (met. a)
Ej.: 059		Sal del ácido 2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]-etanona trifluoroacético	1,28	468,0 (met. a)
Ej.: 060		Hidrocloruro de 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-(3-metoxi-propoxi)-5-(pentafluorosulfanil)fenil]-etanona	0,95	554,2 (met. b)
Ej.: 061		Sal del ácido N,N-dietil-2-[2-(3-terc-butil-4-metoxi-5-morfolin-4-il-fenil)-2-oxoetil]-6-cloro-3-imino-2,3-dihidro-[1,2,4]triazolo[4,3-b]-piridazina-8-carboxamida trifluoroacético	1,29	558,3 (met. a)

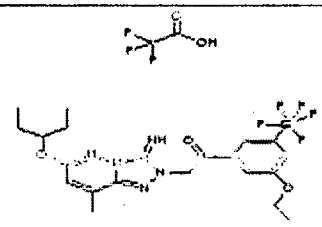
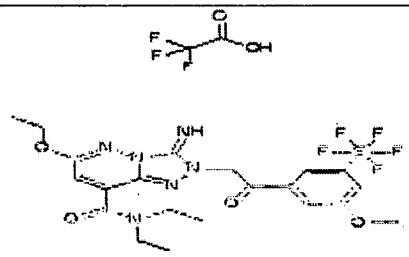
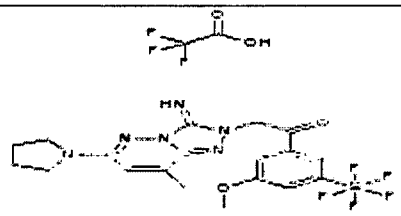
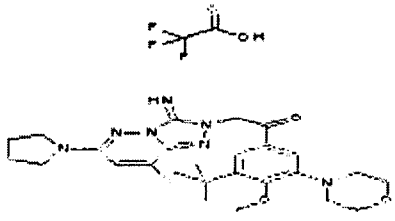
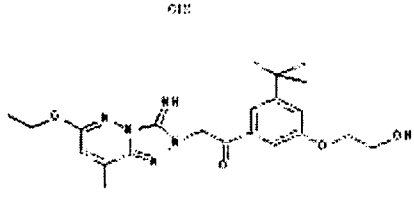
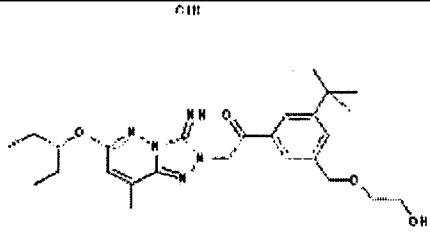
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 062		Sal del ácido N,N-dietil-6-cloro-3-imino-2-{2-[3-metoxi-5-(pentafluorosulfanil)-fenil]-2-oxoetil}-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida trifluoroacético	1,25	543,0 (met. a)
Ej.: 063		Sal del ácido 2-(6-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]-etanona trifluoroacético	1,16	438,0 (met. a)
Ej.: 064		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,27	453,3 (met. a)
Ej.: 065		Hidrocloruro de 1-[3-terc-butil-5-(3-metoxipropoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,52	496,5 (met. a)
Ej.: 066		Hidrocloruro de 1-[3-terc-butil-5-(2-metoxietoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,48	484,4 (met. a)
Ej.: 067		Hidrocloruro de 1-(3-terc-butil-5-ciclopropil-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,63	480,5 (met. a)

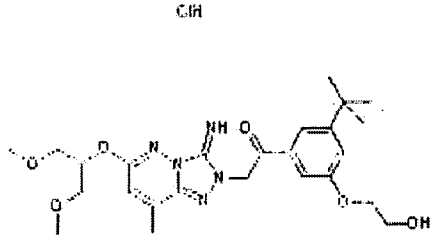
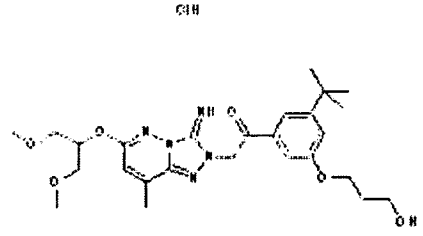
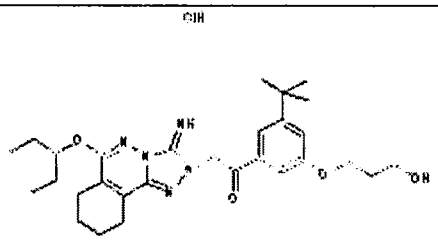
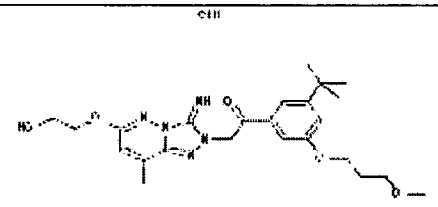
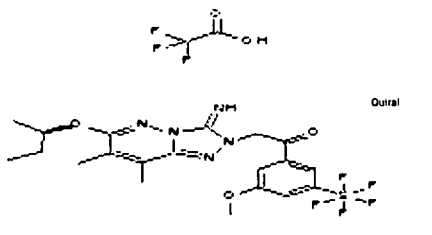
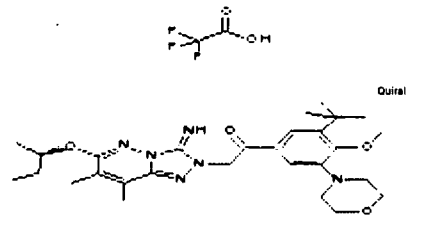
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 068		Hidrocloruro de 1-(3-terc-butil-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,52	440,4 (met. a)
Ej.: 069		Hidrocloruro de 1-[3-terc-butil-5-(3-metoxi-propoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,55	498,5 (met. a)
Ej.: 070		Sal del ácido 2-(6-cloro-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)-fenil]etanona trifluoroacético	1,47	472,1 (met. a)
Ej.: 071		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,57	487,2 (met. a)
Ej.: 072		Sal del ácido N,N-dietil-6-cloro-3-imino-2-{2-[3-metoxi-5-(pentafluorosulfanil)fenil]-2-oxoetil}-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida trifluoroacético	1,47	543,1 (met. a)
Ej.: 073		Sal del ácido N,N-dietil-2-[2-(3-terc-butil-4-metoxi-5-morfolin-4-il-fenil)-2-oxoetil]-6-cloro-3-imino-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida trifluoroacético	1,55	558,3 (met. a)

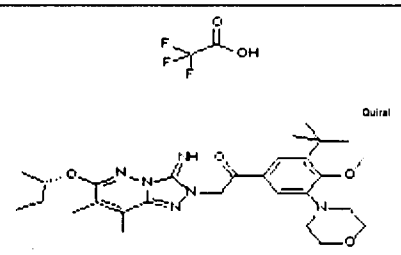
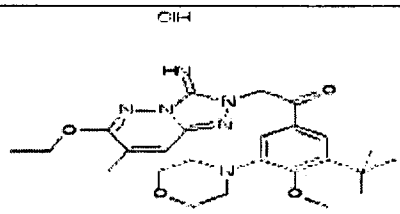
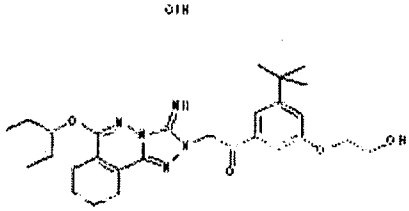
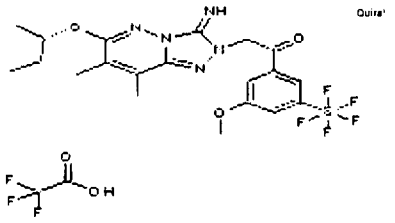
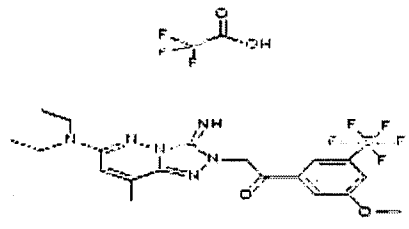
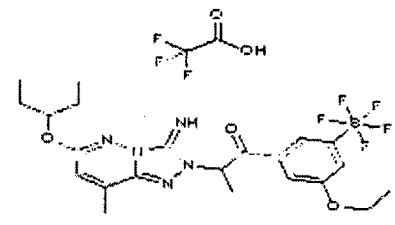
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 074		Hidrocloruro de 1-[3-terc-butil-5-(3-metoxipropoxi)fenil]-2-(6-etoxi-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,89	456,2 (met. b)
Ej.: 075		Hidrocloruro de 1-[3-terc-butil-5-(2-metoxietoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,48	484,5 (met. a)
Ej.: 076		Hidrocloruro 1-(3-terc-butil-5-metoxi-fenil)-2-[6-(1-etilpropoxi)-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	0,83	472,2 (met. b)
Ej.: 077		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-propoximetil)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona	1,38	498,2 (met. a)
Ej.: 078		Sal del ácido N,N-dietil-6-etoxi-3-imino-2-{2-[3-metoxi-5-(pentafluorosulfanil)fenil]-2-oxoetil}-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida trifluoroacético	1,25	553,2 (met. a)
Ej.: 079		Sal del ácido 2-(3-imino-6-metoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)-fenil]etanona trifluoroacético	1,24	468,1 (met. a)

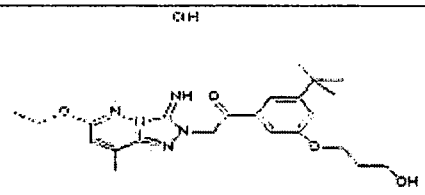
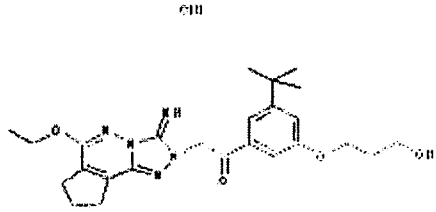
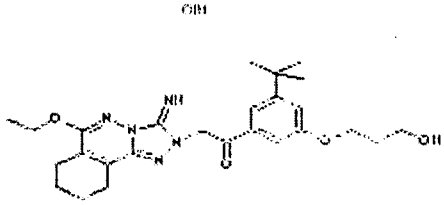
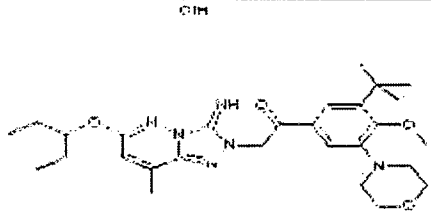
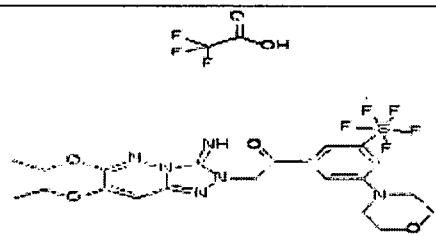
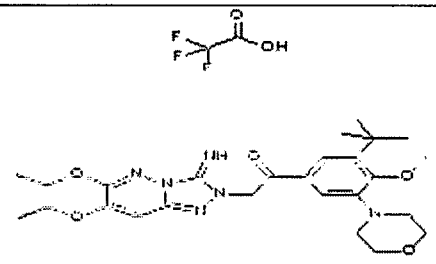
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 080		Sal del ácido 2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)-fenil]etanona trifluoroacético	1,32	482,1 (met. a)
Ej.: 081		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-il-fenil)-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,38	497,2 (met. a)
Ej.: 082		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-7-dietilamino-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,40	530,2 (met. a)
Ej.: 083		Sal del ácido 2-(6-cloro-7-dietilamino-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)-fenil]etanona trifluoroacético	1,32	515,1 (met. a)
Ej.: 084		Sal del ácido 2-(7-dietilamino-6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)-fenil]etanona trifluoroacético	1,65	525,2 (met. a)
Ej.: 085		Sal del ácido 2-[6-(1-etilpropoxi)-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metoxi-5-(pentafluorosulfanil)-fenil]etanona trifluoroacético	1,47	524,2 (met. a)

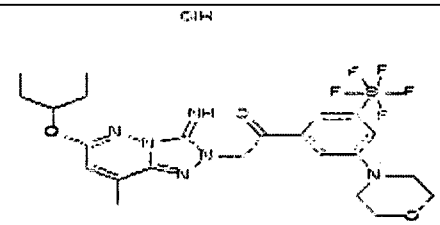
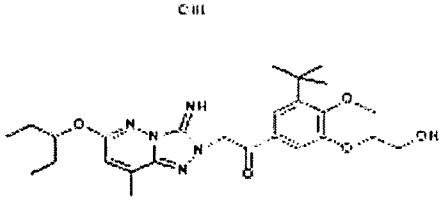
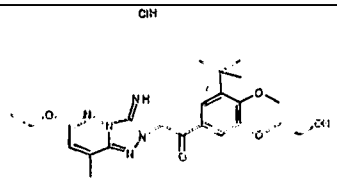
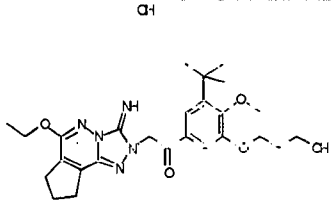
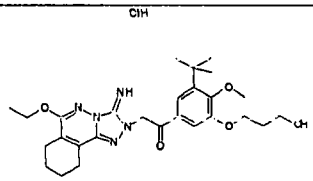
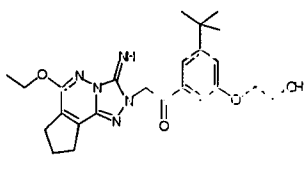
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 086		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[6-(1-etilpropoxi)-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona trifluoroacético	1,52	539,3 (met. a)
Ej.: 087		Sal del ácido N,N-dietil-2-[2-(3-terc-butil-4-metoxi-5-morfolin-4-il-fenil)-2-oxoetil]-6-etoxi-3-imino-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida trifluoroacético	1,32	568,3 (met. a)
Ej.: 088		Sal del ácido N,N-dietil-2-[2-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-oxoetil]-6-etoxi-3-imino-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida trifluoroacético	1,35	568,2 (met. a)
Ej.: 089		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,35	470,2 (met. a)
Ej.: 090		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-propoxi)fenil]-2-[6-(1-etil-propoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,33	484,2 (met. a)
Ej.: 091		Hidrocloruro de 1-[3-terc-butil-5-(3-metoxi-propoxi)fenil]-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo-[4,3-b]piridazin-2-il)etanona	1,34	456,2 (met. a)

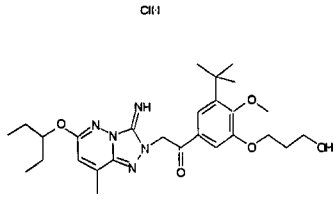
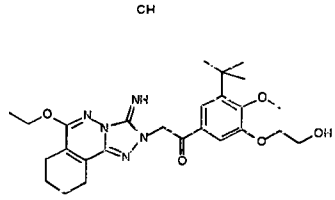
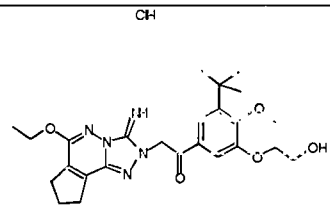
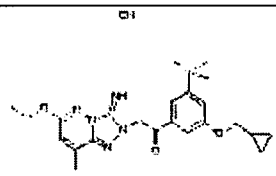
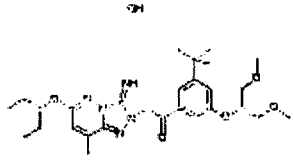
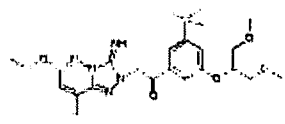
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 092		Sal del ácido 1-[3-etoxi-5-(pentafluoro-sulfanil)fenil]-2-[6-(1-etil-propoxi)-3-imino-8-metil-[1,2,4]triazolo-[4,3-b]piridazin-2-il]etanona trifluoroacético	1,47	524,2 (met. a)
Ej.: 093		Sal del ácido N,N-dietil-6-etoxi-3-imino-2-{2-[3-metoxi-5-(pentafluoro-sulfanil)fenil]-2-oxoetil}-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida trifluoroacético	1,28	553,2 (met. a)
Ej.: 094		Sal del ácido 2-(3-imino-8-metil-6-pirrolidin-1-il-[1,2,4]triazolo-[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluoro-sulfanil)fenil]etanona trifluoroacético	1,27	493,1 (met. a)
Ej.: 095		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-8-metil-6-pirrolidin-1-il-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona trifluoroacético	1,36	508,3 (met. a)
Ej.: 096		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoxi)fenil]-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo-[4,3-b]piridazin-2-il)etanona	1,16	428,3 (met. a)
Ej.: 097		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoximetil)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,34	464,2 (met. a)

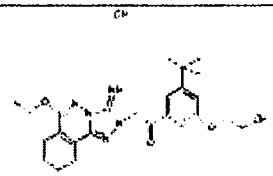
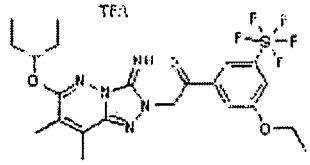
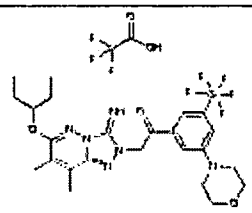
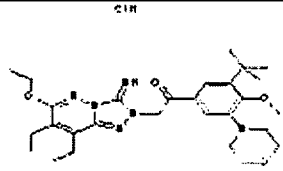
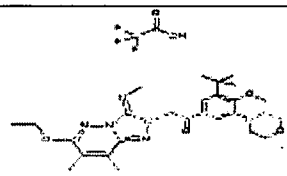
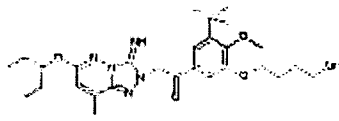
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 098		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoxi)fenil]-2-[3-imino-6-(2-metoxi-1-metoximetil-etoxi)-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,15	502,2 (met. a)
Ej.: 099		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-propoxi)fenil]-2-[3-imino-6-(2-metoxi-1-metoximetil-etoxi)-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,21	516,3 (met. a)
Ej.: 100		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-propoxi)fenil]-2-[6-(1-etil-propoxi)-3-imino-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]ftalazin-2-il]etanona	0,99	524,3 (met. b)
Ej.: 101		Hidrocloruro de 1-[3-terc-butil-5-(3-metoxi-propoxi)fenil]-2-[6-(2-hidroxi-etoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,24	472,2 (met. a)
Ej.: 102		Sal del ácido 2-[6-((R)-sec-butoxi)-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metoxi-5-(pentafluorosulfanil)fenil]-trifluoroacético	1,05	510,2 (met. b)
Ej.: 103		Sal del ácido 2-[6-((R)-sec-butoxi)-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(3-terc-butil-4-metoxi-5-morfolin-4-il-fenil)etanona trifluoroacético	1,08	525,4 (met. b)

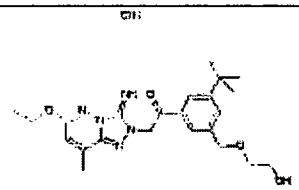
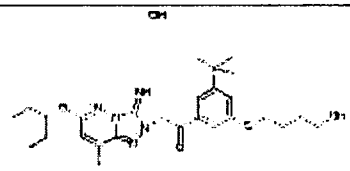
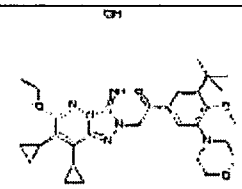
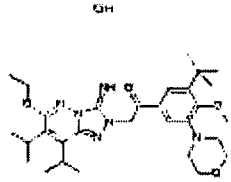
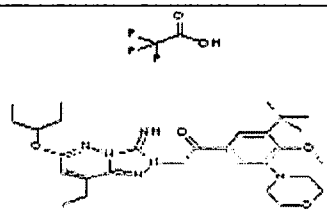
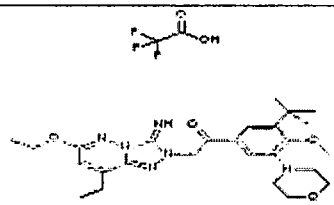
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 104		Sal del ácido 2-[6-((R)-sec-butoxi)-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(3-terc-butil-4-metoxi-5-morfolin-4-il-fenil)etanona trifluoroacético	1,08	525,4 (met. b)
Ej.: 105		Hidrocloruro de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,38	483,3 (met. a)
Ej.: 106		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoxi)fenil]-2-[6-(1-etil-propoxi)-3-imino-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]ftalazin-2-il]etanona	1,48	510,3 (met. a)
Ej.: 107		Hidrocloruro de 2-[6-((S)-sec-butoxi)-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metoxi-5-(pentafluorosulfanil)fenil]-etanona	1,05	510,2 (met. b)
Ej.: 108		Sal del ácido 2-(6-dietilamino-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]-etanona trifluoroacético	1,01	495,2 (met. b)
Ej.: 109		Sal del ácido 1-[3-etoxi-5-(pentafluoro-sulfanil)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]propan-1-ona trifluoroacético	1,07	538,2 (met. b)

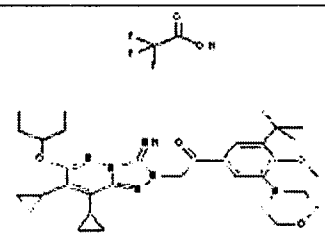
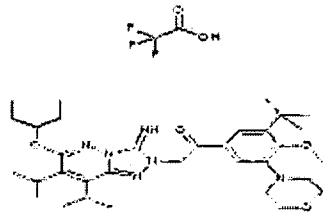
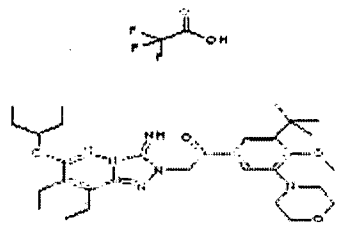
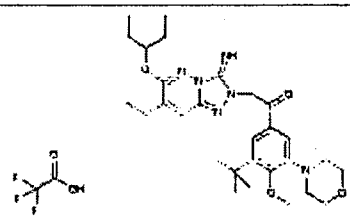
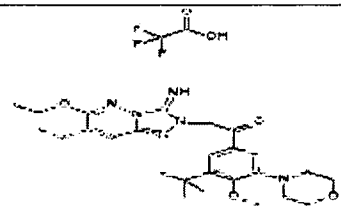
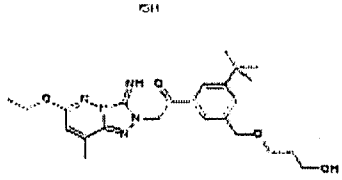
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 110		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-propoxi)fenil]-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,23	442,3 (met. a)
Ej.: 111		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-propoxi)fenil]-2-(6-etoxi-3-imino-8,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,3	468,2 (met. a)
Ej.: 112		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-propoxi)fenil]-2-(6-etoxi-3-imino-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]ftalazin-2-il)etanona	1,36	482,2 (met. a)
Ej.: 113		Hidrocloruro de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona	1,53	525,3 (met. a)
Ej.: 114		Sal del ácido 2-(6,7-dietoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-morfolin-4-il-5-(pentafluorosulfanil)fenil]-etanona trifluoroacético	0,91	553,2 (met. b)
Ej.: 115		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6,7-dietoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,01	513,4 (met. b)

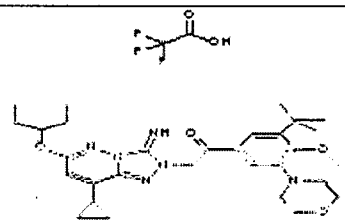
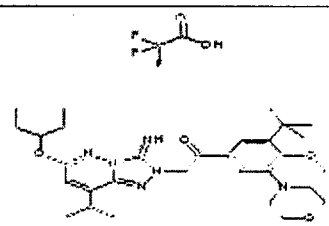
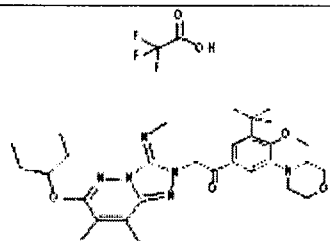
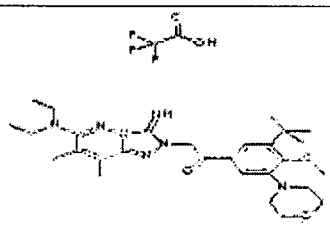
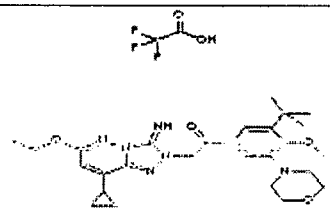
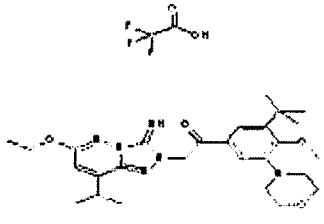
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 116		Hidrocloruro de 2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-morfolin-4-il-5-(pentafluorosulfanil)fenil]-etanona	1,05	565,3 (met. b)
Ej.: 117		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoxi)-4-metoxifenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona	1,38	500,3 (met. a)
Ej.: 118		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,19	458,3 (met. a)
Ej.: 119		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-6,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,32	498,2 (met. a)
Ej.: 120		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]ftalazin-2-il)etanona	1,38	512,3 (met. a)
Ej.: 121		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-etoxi-3-imino-6,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,24	454,2 (met. a)

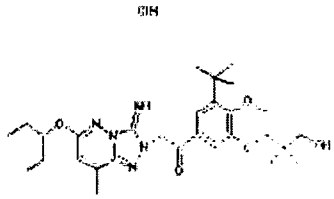
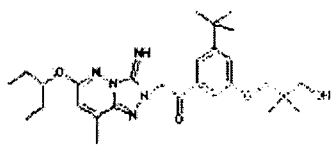
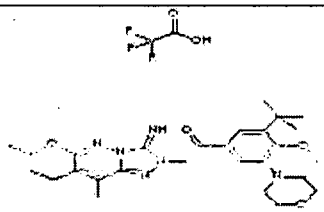
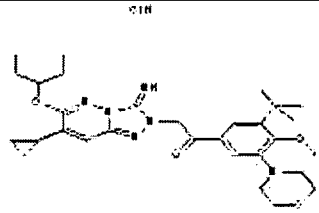
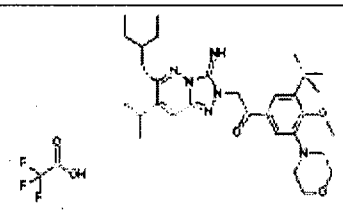
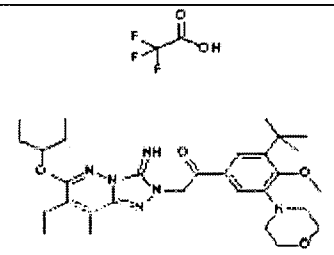
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 122		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,41	514,2 (met. a)
Ej.: 123		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]-ftalazin-2-il)etanona	1,27	498,2 (met. a)
Ej.: 124		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-8,9-dihidro-7H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,21	484,2 (met. a)
Ej.: 125		Hidrocloruro de 1-(3-terc-butil-5-ciclopropil-metoxifenil)-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo-[4,3-b]piridazin-2-il)etanona	1,4	438,3 (met. a)
Ej.: 126		Hidrocloruro de 1-[3-terc-butil-5-(2-metoximetiletoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona	1,46	528,3 (met. a)
Ej.: 127		Hidrocloruro de 1-[3-terc-butil-5-(2-metoxi-1-metoximetiletoxi)fenil]-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,31	486,2 (met. a)

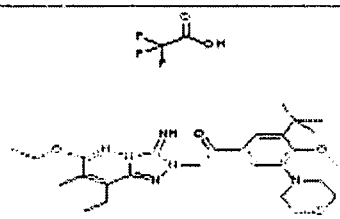
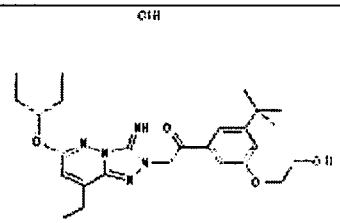
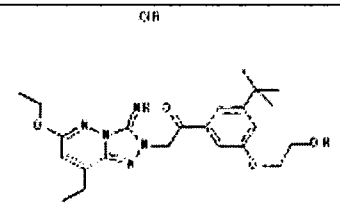
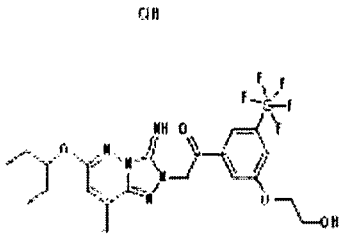
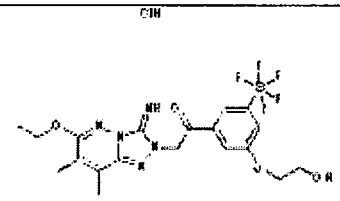
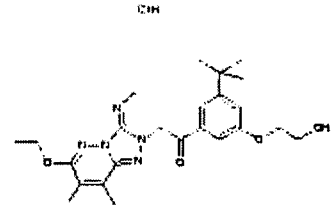
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 128		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoxi)fenil]-2-(6-etoxi-3-imino-7,8,9,10-tetrahidro-[1,2,4]triazolo[3,4-a]ftalazin-2-il)etanona	1,3	468,2 (met. a)
Ej.: 129		Sal del ácido 1-[3-etoxi-5-(pentafluoro-sulfanil)fenil]-2-[6-(1-etilpropoxi)-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona trifluoroacético	1,1	538,2 (met. b)
Ej.: 130		Sal de ácido 2-[6-(1-etilpropoxi)-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il-1-[3-morfolin-4-il-5-(pentafluorosulfanil)-fenil]etanona trifluoroacético	1,05	565,3 (met. b)
Ej.: 131		Hidrocloruro de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-7,8-dietil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,09	525,4 (met. b)
Ej.: 132		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-{6-etoxi-7,8-dimetil-3-[(E)-metilimino]-[1,2,4]triazolo[4,3-b]piridazin-2-il}etanona trifluoroacético	1,06	511,4 (met. b)
Ej.: 133		Hidrocloruro de 1-[3-terc-butil-5-(4-hidroxibutoxi)-4-metoxifenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,42	528,3 (met. a)

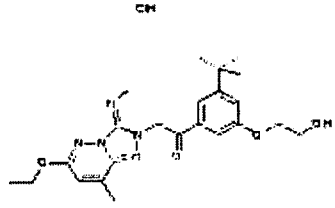
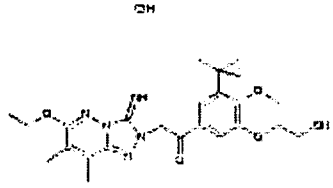
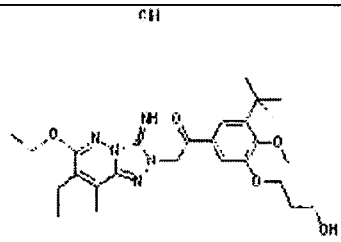
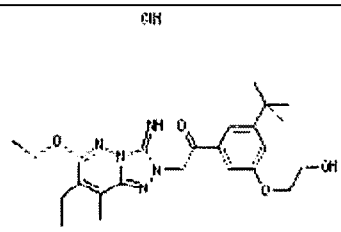
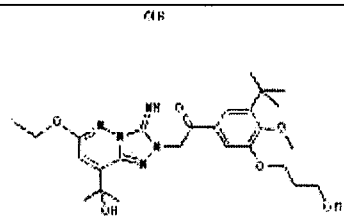
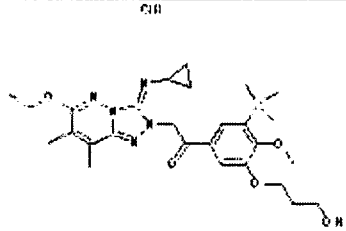
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 134		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoximetil)fenil]-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,16	442,3 (met. a)
Ej.: 135		Hidrocloruro de 1-[3-terc-butil-5-(4-hidroxibutoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,4	498,2 (met. a)
Ej.: 136		Hidrocloruro de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(7,8-diciclopropil-6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,11	549,4 (met. b)
Ej.: 137		Hidrocloruro de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-3-imino-7,8-diisopropil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,15	553,4 (met. b)
Ej.: 138		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[8-etil-6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona trifluoroacético	1,11	539,4 (met. b)
Ej.: 139		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-8-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,04	497,3 (met. b)

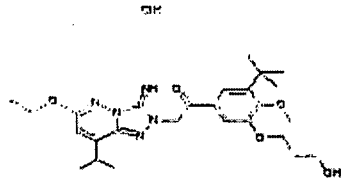
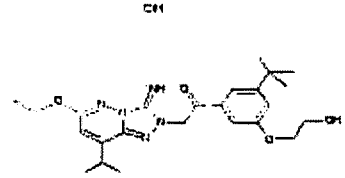
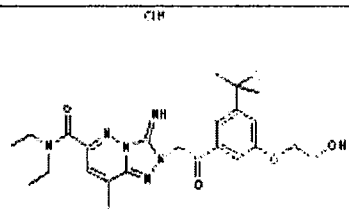
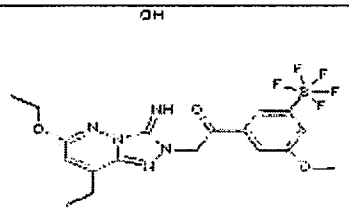
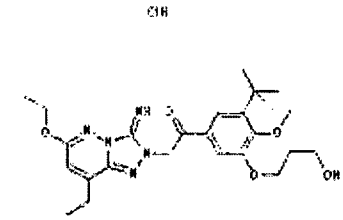
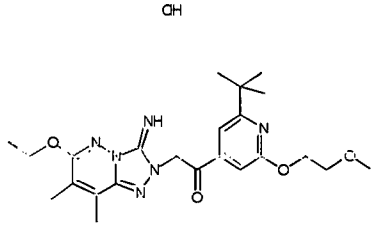
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 140		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[7,8-diciclopropil-6-(1-etil-propoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona trifluoroacético	1,16	591,4 (met. b)
Ej.: 141		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[6-(1-etilpropoxi)-3-imino-7,8-diisopropil-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona trifluoroacético	1,19	595,5 (met. b)
Ej.: 142		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[7,8-dietil-6-(1-etil-propoxi)-3-imino-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona trifluoroacético	1,15	567,4 (met. b)
Ej.: 143		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[7-etil-6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona trifluoroacético	1,11	539,4 (met. b)
Ej.: 144		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-7-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,04	497,3 (met. b)
Ej.: 145		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-propoximetil)fenil]-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,19	456,2 (met. a)

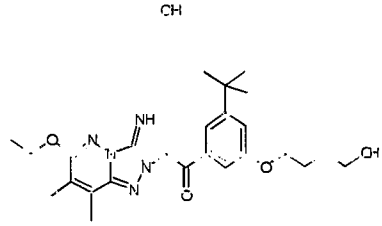
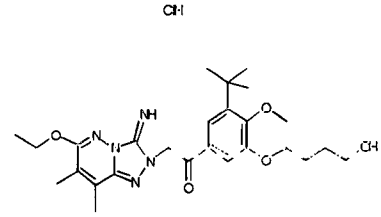
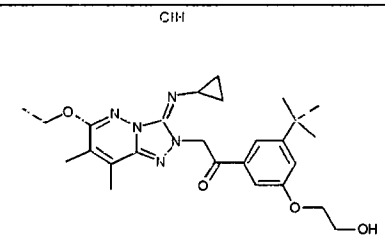
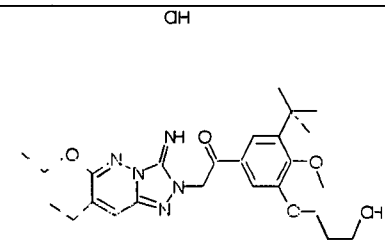
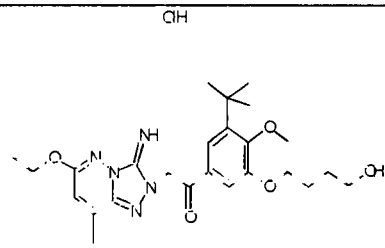
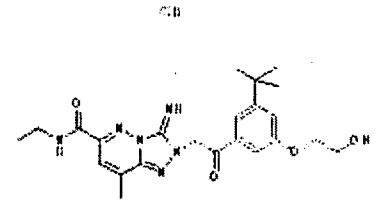
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 146		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[8-ciclopropil-6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona trifluoroacético	1,11	551,4 (met. b)
Ej.: 147		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[6-(1-etilpropoxi)-3-imino-8-isopropil-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona trifluoroacético	1,13	553,4 (met. b)
Ej.: 148		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-{6-(1-etilpropoxi)-7,8-dimetil-3-[(E)-metilimino]-[1,2,4]triazolo-[4,3-b]piridazin-2-il}etanona trifluoroacético	1,12	553,4 (met. b)
Ej.: 149		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-dietilamino-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona trifluoroacético	1,08	524,4 (met. b)
Ej.: 150		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(8-ciclopropil-6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,05	509,3 (met. b)
Ej.: 151		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-3-imino-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,07	511,4 (met. b)

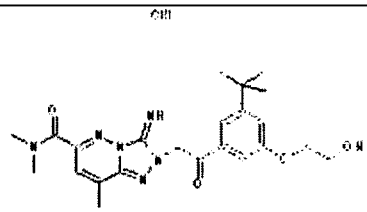
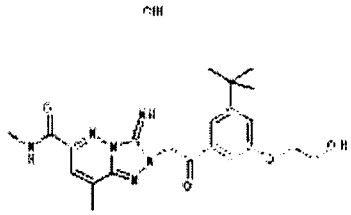
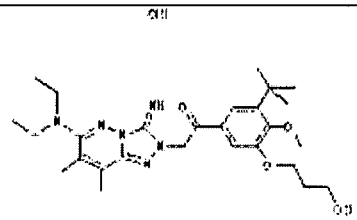
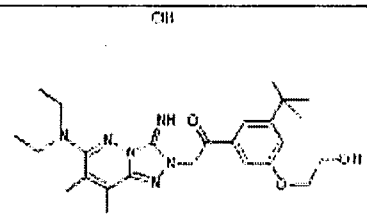
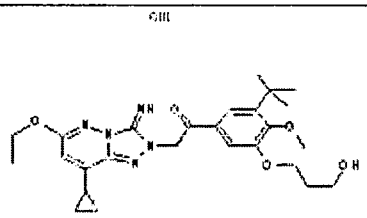
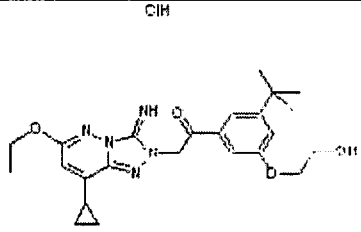
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 152		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-2,2-dimetilpropoxi)-4-metoxi-fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo-[4,3-b]piridazin-2-il]etanona	1,5	542,3 (met. a)
Ej.: 153		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-2,2-dimetilpropoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,48	512,3 (met. a)
Ej.: 154		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-7-etil-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,07	511,4 (met. b)
Ej.: 155		Hidrocloruro de 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[7-ciclopropil-6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,12	551,4 (met. b)
Ej.: 156		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[6-(1-etilpropoxi)-3-imino-7-isopropil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona trifluoroacético	1,13	553,4 (met. b)
Ej.: 157		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[7-etil-6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona trifluoroacético	1,14	553,4 (met. b)

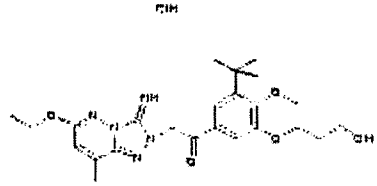
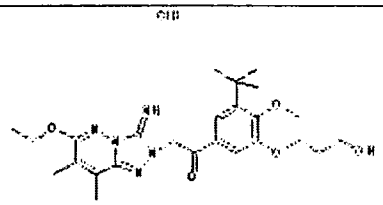
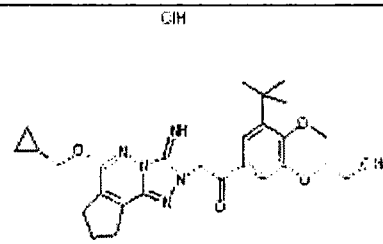
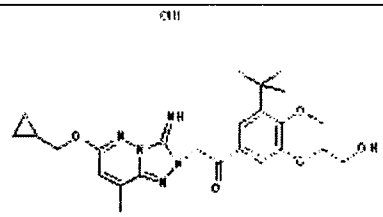
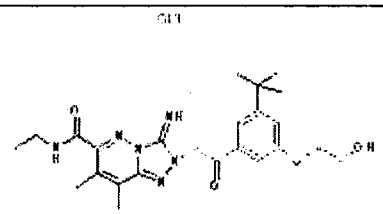
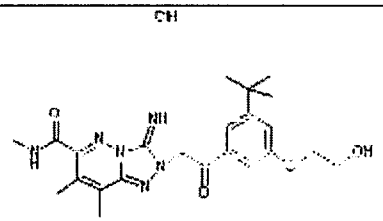
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 158		Sal del ácido 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-8-etil-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona trifluoroacético	1,07	511,4 (met. b)
Ej.: 159		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-[8-etil-6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,03	484,4 (met. b)
Ej.: 160		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoxi)fenil]-2-(6-etoxi-8-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,95	442,3 (met. b)
Ej.: 161		Sal del ácido 2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-(2-hidroxietoxi)-5-(pentafluorosulfanil)-fenil]etanona trifluoroacético	0,89	540,2 (met. b)
Ej.: 162		Hidrocloruro de 2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-(2-hidroxietoxi)-5-(pentafluorosulfanil)-fenil]etanona	1,23	512,2 (met. a)
Ej.: 163		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-{6-etoxi-7,8-dimetil-3-[(E)-metilimino]-[1,2,4]triazolo[4,3-b]piridazin-2-il}etanona	0,97	456,3 (met. b)

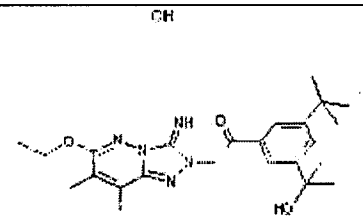
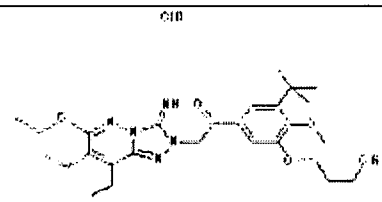
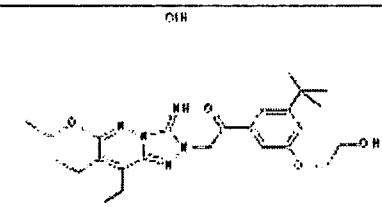
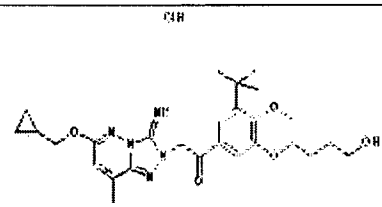
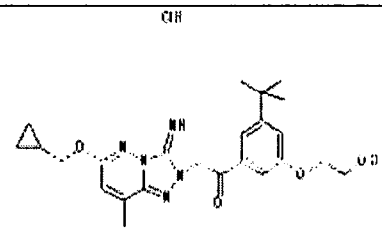
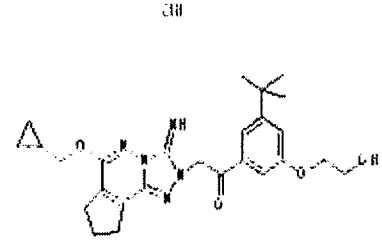
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 164		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-etoxi-8-metil-3-[(E)-metilimino]-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,94	442,3 (met. b)
Ej.: 165		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,83	472,2 (met. b)
Ej.: 166		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-7-etil-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,03	500,3 (met. b)
Ej.: 167		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-etoxi-7-etil-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,98	456,3 (met. b)
Ej.: 168		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-[6-etoxi-8-(1-hidroxi-1-metil-etil)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	0,96	516,3 (met. b)
Ej.: 169		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(3-[(E)-ciclopropilimino]-6-etoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,04	526,4 (met. b)

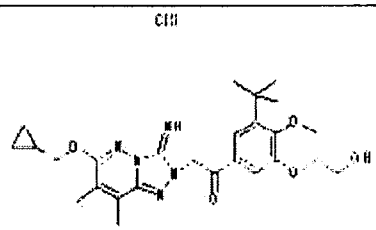
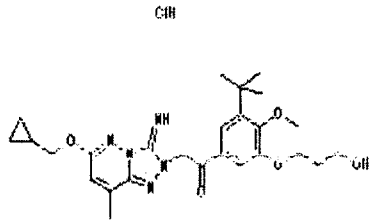
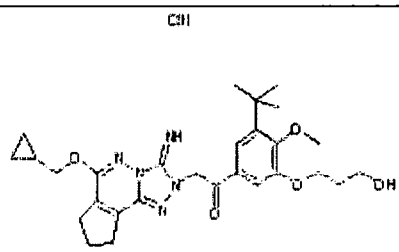
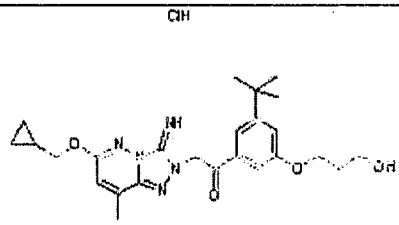
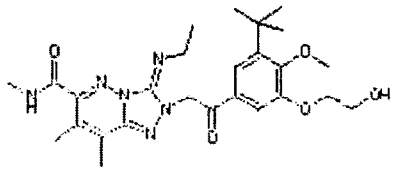
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 170		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,03	500,3 (met. b)
Ej.: 171		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-etoxi-3-imino-8-isopropil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,00	456,3 (met. b)
Ej.: 172		Hidrocloruro de N,N-dietil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-oxoetil}-3-imino-8-metil-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida	0,74	483,3 (met. b)
Ej.: 173		Hidrocloruro de 2-(6-etoxi-8-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]-etanona	1,02	482,2 (met. b)
Ej.: 174		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-8-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,00	486,3 (met. b)
Ej.: 175		Hidrocloruro de 1-[2-terc-butil-6-(2-metoxi-etoxi)piridin-4-il]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,83	472,2 (met. b)

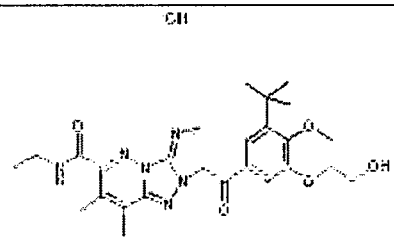
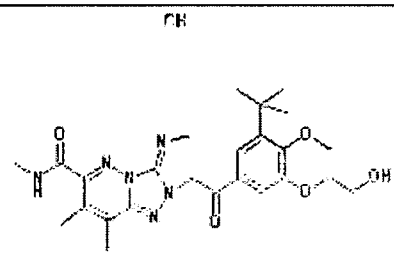
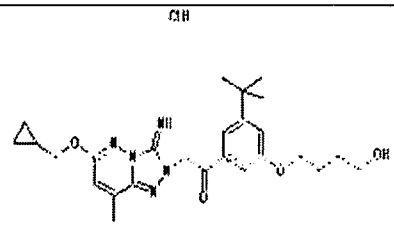
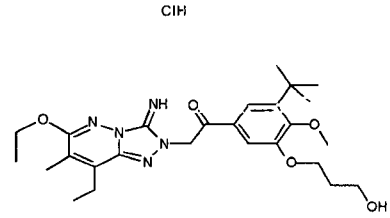
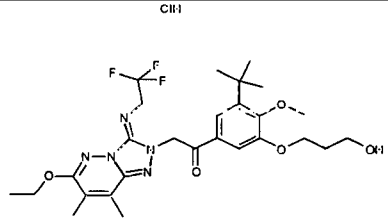
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 176		Hidrocloruro de 1-[3-terc-butil-5-(4-hidroxibutoxi)fenil]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,82	470,2 (met. b)
Ej.: 178		Hidrocloruro de 1-[3-terc-butil-5-(4-hidroxibutoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,86	500,3 (met. b)
Ej.: 179		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi etoxi)fenil]-2-(3-[(E)-ciclopropilimino]-6-etoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,99	482,3 (met. b)
Ej.: 180		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-7-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,99	486,3 (met. b)
Ej.: 181		Hidrocloruro de 1-[3-terc-butil-5-(4-hidroxibutoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,86	482,2 (met. b)
Ej.: 182		Hidrocloruro de N-etil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-oxo-etil}-3-imino-8-metil-2,3-dihidro-[1,2,4]triazolo[4,3-b]-piridazina-6-carboxamida	0,74	455,2 (met. b)

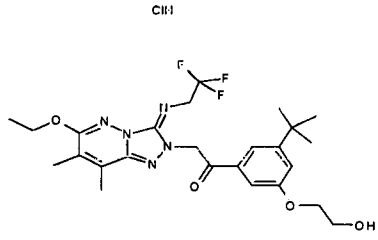
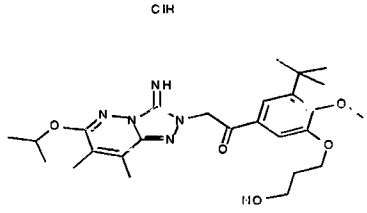
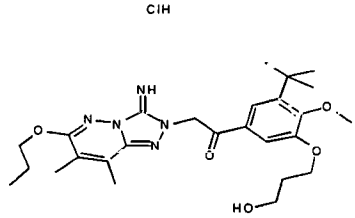
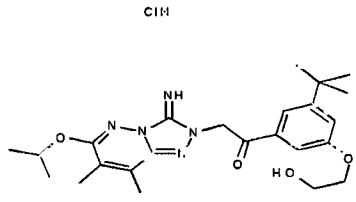
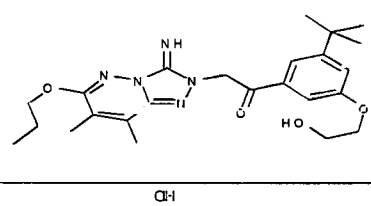
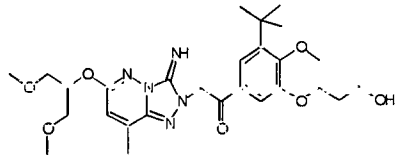
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 183		Hidrocloruro de N,N-dimetil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-oxo-etil}-3-imino-8-metil-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida	0,7	455,3 (met. b)
Ej.: 184		Hidrocloruro de N-metil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-oxo-etil}-3-imino-8-metil-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida	0,7	441,2 (met. b)
Ej.: 186		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-dietilamino-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,02	513,4 (met. b)
Ej.: 187		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-dietilamino-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,98	468,4 (met. b)
Ej.: 188		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(8-ciclopropil-6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,00	498,3 (met. b)
Ej.: 189		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(8-ciclopropil-6-etoxi-3-imino-[1,2,4]triazolo-[4,3-b]piridazin-2-il)etanona	0,96	454,3 (met. b)

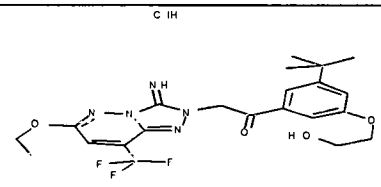
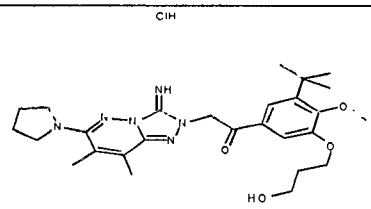
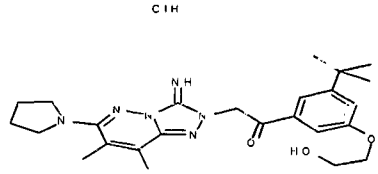
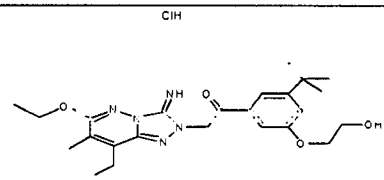
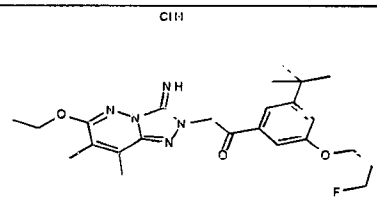
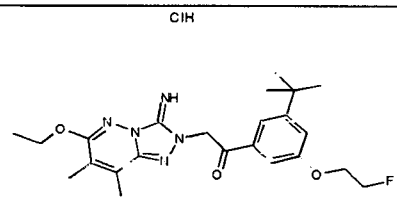
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 190		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,82	472,2 (met. b)
Ej.: 191		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,85	486,2 (met. b)
Ej.: 192		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-(6-ciclopropilmetoxi-3-imino-8,9-dihidro-7H-ciclopenta[d]-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,89	510,2 (met. b)
Ej.: 193		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-(6-ciclopropilmetoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona	0,83	484,2 (met. b)
Ej.: 194		Hidrocloruro de N-etil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-oxo-etil}-3-imino-7,8-dimetil-2,3-dihidro-[1,2,4]triazolo[4,3-b]-piridazina-6-carboxamida	0,78	469,2 (met. b)
Ej.: 195		Hidrocloruro de N-metil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-oxo-etil}-3-imino-7,8-dimetil-2,3-dihidro-[1,2,4]triazolo-[4,3-b]-piridazina-6-carboxamida	0,71	455,3 (met. b)

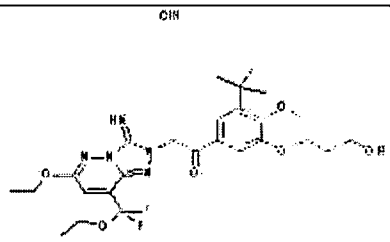
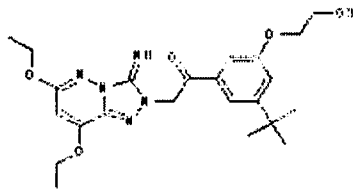
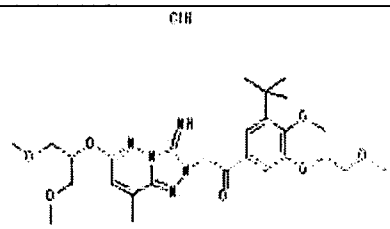
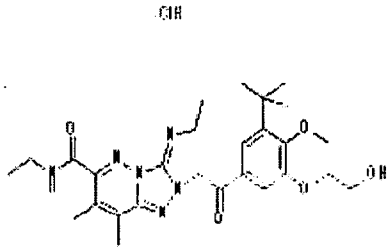
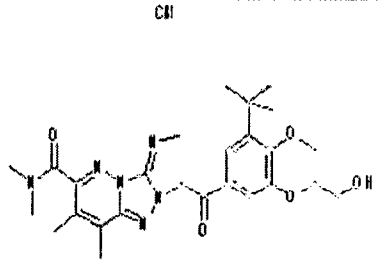
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 196		Hidrocloruro de 1-[3-terc-butil-5-(1-hidroxi-1-metiletil)fenil]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona	0,98	440,3 (met. b)
Ej.: 197		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-7,8-dietil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,06	514,4 (met. b)
Ej.: 198		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoxi)fenil]-2-(6-etoxi-7,8-dietil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,02	470,3 (met. b)
Ej.: 199		Hidrocloruro de 1-[3-terc-butil-5-(4-hidroxibutoxi)-4-metoxifenil]-2-(6-ciclopropilmetoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,87	512,3 (met. b)
Ej.: 200		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxi-etoxi)fenil]-2-(6-ciclopropilmetoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,81	454,2 (met. b)
Ej.: 201		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-ciclopropilmetoxi-3-imino-8,9-dihidro-7H-ciclopenta[d]-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,85	480,2 (met. b)

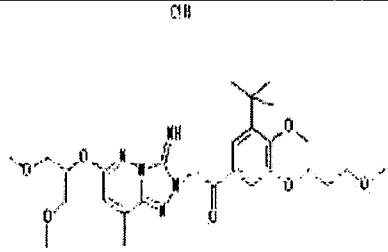
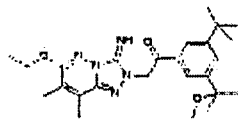
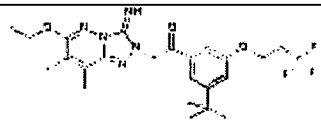
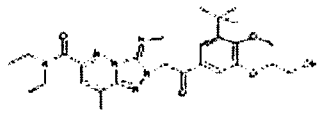
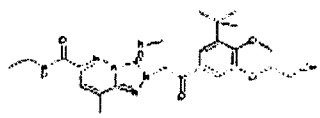
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 202		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-(6-ciclopropilmetoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,87	498,2 (met. b)
Ej.: 203		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-ciclopropilmetoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona	0,86	498,2 (met. b)
Ej.: 204		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-ciclopropilmetoxi-3-imino-8,9-dihidro-7H-ciclopenta[d]-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,88	524,3 (met. b)
Ej.: 205		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)fenil]-2-(6-ciclopropilmetoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,83	468,2 (met. b)
Ej.: 206		Hidrocloruro de N-metil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-oxoetil}-3-[(E)-etilimino]-7,8-dimetil-2,3-dihidro-[1,2,4]triazolo[4,3-b]-piridazina-6-carboxamida	0,76	513,3 (met. b)

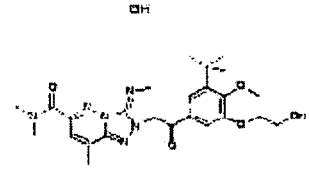
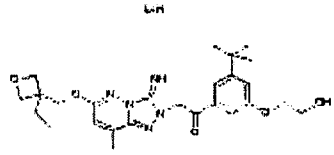
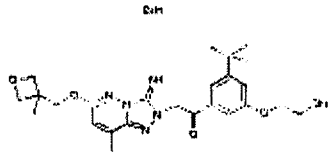
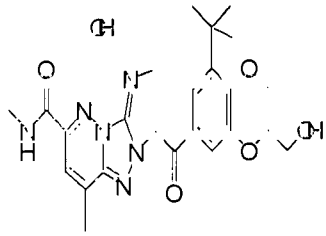
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 207		Hidrocloruro de N-etil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-oxoetil}-7,8-dimetil-3-[(E)-metilimino]-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida	0,77	513,3 (met. b)
Ej.: 208		Hidrocloruro de N-metil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-oxoetil}-7,8-dimetil-3-[(E)-metilimino]-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida	0,75	499,2 (met. b)
Ej.: 209		Hidrocloruro de 1-[3-terc-butil-5-(4-hidroxibutoxi)fenil]-2-(6-ciclopropilmetoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,85	482,2 (met. b)
Ej.: 210		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(6-etoxi-8-etil-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,02	500,4 (met. b)
Ej.: 211		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-{6-etoxi-7,8-dimetil-3-[(E)-2,2,2-trifluoroetilimino]-[1,2,4]triazolo[4,3-b]piridazin-2-il}etanona	1,04	568,3 (met. b)

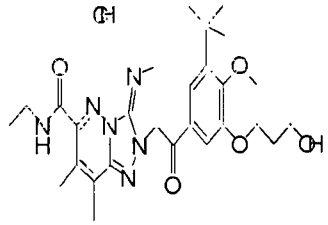
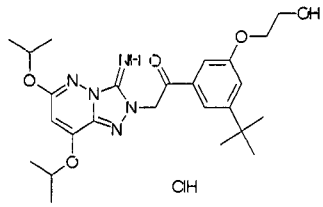
		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 212		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-etoxi-7,8-dimetil-3-[(E)-2,2,2-trifluoroetilimino]-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,01	524,3 (met. b)
Ej.: 213		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-etoxi-7,8-dimetil-3-[(E)-2,2,2-trifluoro-etilimino]-[1,2,4]triazolo[4,3-b]piridazin-2-il}etanona	1,02	500,4 (met. b)
Ej.: 214		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxi-propoxi)-4-metoxifenil]-2-(3-imino-7,8-dimetil-6-propoxi-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,02	500,3 (met. b)
Ej.: 215		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(3-imino-6-isopropoxi-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,98	456,3 (met. b)
Ej.: 216		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(3-imino-7,8-dimetil-6-propoxi-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,98	456,3 (met. b)
Ej.: 217		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-[3-imino-6-(2-metoxi-1-metoximetiletoxi)-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	0,8	546,3 (met. b)

		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 218		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-etoxi-3-imino-8-trifluorometil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,97	482,3 (met. b)
Ej.: 219		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-(3-imino-7,8-dimetil-6-pirrolidin-1-il-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona	1,01	511,4 (met. b)
Ej.: 220		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(3-imino-7,8-dimetil-6-pirrolidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,97	467,3 (met. b)
Ej.: 221		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6-etoxi-8-etil-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,97	456,3 (met. b)
Ej.: 222		Hidrocloruro de 1-[3-terc-butil-5-(3-fluoro-propoxi)fenil]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,04	458,3 (met. b)
Ej.: 223		Hidrocloruro de 1-[3-terc-butil-5-(2-fluoroetoxi)fenil]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	1,02	444,3 (met. b)

		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 224		Hidrocloruro de 1-[3-terc-butil-5-(3-hidroxipropoxi)-4-metoxifenil]-2-[6-etoxi-8-(etoxidifluorometil)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	1,02	552,3 (met. b)
Ej.: 225		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-(6,8-dietoxi-3-imino-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona	0,82	458,2 (met. b)
Ej.: 226		Hidrocloruro de 1-[3-terc-butil-4-metoxi-5-(2-metoxietoxi)fenil]-2-[3-imino-6-(2-metoxi-1-metoximetiletoxi)-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	0,85	546,3 (met. b)
Ej.: 227		Hidrocloruro de N-etil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-oxoetil}-3-[(E)-etilimino]-7,8-dimetil-2,3-dihidro-[1,2,4]triazolo[4,3-b]-piridazina-6-carboxamida	0,78	527,2 (met. b)
Ej.: 228		Hidrocloruro de N,N-dimetil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxi-fenil]-2-oxoetil}-7,8-dimetil-3-[(E)-metilimino]-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida	0,75	513,3 (met. b)

		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 229		Hidrocloruro de 1-[3-terc-butil-4-metoxi-5-(3-metoxipropoxi)fenil]-2-[3-imino-6-(2-metoxi-1-metoximetiletoxi)-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona	0,88	560,3 (met. b)
Ej.: 230		Hidrocloruro de 1-[3-terc-butil-5-(1-metoxi-1-metiletil)fenil]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,99	454,3 (met. b)
Ej.: 231		Hidrocloruro de 1-[3-terc-butil-5-(3,3,3-trifluoro-propoxi)fenil]-2-(6-etoxi-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona	0,98	494,2 (met. b)
Ej.: 232		Hidrocloruro de N,N-dietil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-oxoetil}-8-metil-3-[(E)-metilimino]-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida	0,78	527,2 (met. b)
Ej.: 233		Hidrocloruro de N-etil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-oxoetil}-8-metil-3-[(E)-metilimino]-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida	0,77	499,2 (met. b)

		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 234		Hidrocloruro de N,N-dimetil-2-{2-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxi-fenil]-2-oxoetil}-8-metil-3-[(E)-metilimino]-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-6-carboxamida	0,74	499,2 (met. b)
Ej.: 235		Hidrobromuro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-[6-(3-etil-oxetan-3-ilmetoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona	0,78	498,2 (met. b)
Ej.: 236		Hidrobromuro de 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-[3-imino-8-metil-6-(3-metiloxetan-3-ilmetoxi)-[1,2,4]triazolo[4,3-b]-piridazin-2-il]etanona	0,75	484,2 (met. b)
Ej.: 237		Sal del ácido 1-[3-terc-butil-5-(2-hidroxietoxi)fenil]-2-[3-imino-8-metil-6-(oxetan-3-iloxi)-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona acético	0,73	456,2 (met. b)
Ej.: 238		Hidrocloruro de metilamida del ácido 2-{2-[3-terc-butil-5-(2-hidroxietoxi)-4-metoxifenil]-2-oxo-etil}-8-metil-3-[(E)-metilimino]-2,3-dihidro-1,2,4]triazolo[4,3-b]piridazina-6-carboxílico	0,76	485,2 (met. b)

		Nombre	Tr de LCMS [min]	$[M+H^+]^+$
Ej.: 239		Hidrocloruro de metilamida del ácido 2-{2-[3-terc-butil-5-(2-hidroxi-etoxi)-4-metoxifenil]-2-oxo-etil}-8-metil-3-[(E)-metilimino]-2,3-dihidro-1,2,4]triazolo[4,3-b]piridazina-6-carboxílico	0,80	527,2 (met. b)
Ej.: 240		Hidrocloruro de 1-[3-terc-butil-5-(2-hidroxietoxi)-fenil]-2-(3-imino-6,8-diisopropoxi-[1,2,4]triazolo[4,3-b]piridazin-2-il)-etanona	0,90	486,3 (met. b)

Ejemplos farmacológicos

Método de determinación de PAR1: Inhibición de la agregación plaquetaria mediada por PAR1

El ensayo farmacológico de las sustancias se llevó a cabo en la agregación plaquetaria inducida por TRAP (péptido activador del receptor de trombina, por sus siglas en inglés) en un formato de 96 pocillos. Para este fin, se tomó sangre a partir de donantes voluntarios sanos en jeringas de 20 ml que contenían 2 ml de solución de citrato sódico al 3,13%. Después de una centrifugación de 20 minutos a 150 x g, el plasma rico en plaquetas (PRP) se separó y se mezcló con 1 µl de disolución de PEG1 (500 µg/ml en etanol)/ml de PRP. La incubación a TA durante 5 minutos se continuó de centrifugación a 120 x g durante 15 minutos para retirar los leucocitos. El PRP libre de leucocitos se transfirió en partes de 5 ml a tubos de PP de 15 ml y se centrifugó a 360xg durante 15 minutos para sedimentar las plaquetas. Posteriormente, el plasma se decantó y el sedimento de plaquetas procedente de 5 ml de PRP se resuspendió en 1 ml de Tyrode (NaCl 120 mM, KCl 2,6 mM, $NaHCO_3$ 12 mM, $NaH_2PO_4 \times H_2O$ 0,39 mM, HEPES 10 mM, BSA al 0,35%, glucosa 5,5 mM, pH 7,4) y se ajustó con Tyrode hasta un recuento de plaquetas de 3×10^5/microlitro (µl). Después se mezclaron 13 ml de esta suspensión celular con 866 µl de solución

de $CaCl_2$ 10 mM y se pipetearon 120 µl en cada pocillo de una placa de 96 pocillos que contenía 15 µl de la sustancia a ensayar. Después de la incubación a temperatura ambiente en la oscuridad durante 30 minutos, se añadieron 15 µl de una disolución de TRAP (70-100 µM) como agonista y se registró la cinética a 37ºCdurante 20 minutos en un SpectraMax 340 a 650 nm mientras se agitaba. Se calcularon las áreas bajo las curvas de control negativo (Tyrode/ DMSO) y control positivo (15 µl de agonista/DMSO) y la diferencia se fijó como el valor de 100%. Se pipetearon las sustancias que se iban a ensayar como una dilución seriada en una determinación duplicada, asimismo se determinó el AUCde cada concentración de la sustancia y se calculó el % de inhibición del AUCen comparación con el control. Basándose en el % de inhibición, el valor de CI_{50} se calculó por un análisis de regresión no lineal de acuerdo con la ecuación de 4 parámetros.

La tabla 1 muestra los resultados.

Tabla 1:

Compuesto del ejemplo	Inhibición de la agregación plaquetaria CI_{50} [micro M]	Compuesto del ejemplo	Inhibición de la agregación plaquetaria CI_{50} [micro M]
1	0,65	2	1,6
5	8,5	7	0,158
16	0,127	66	0,025
77	0,009	85	0,059
90	0,012	98	0,334
108	0,016		

Ensayo de unión a PAR1

Las sustancias sintetizadas se examinaron en un ensayo de unión a PAR1. Éste ensayó si las sustancias pueden inhibir la unión de un agonista de PAR1 marcado radiactivamente conocido en la bibliografía en el receptor PAR1 (Ho-Sam Ahn, Mol Pharm, 51:350-356, 1997).

El receptor PAR1 humano se expresó de manera transitoria en células de insecto High Five. A partir de estas células, después de 48 horas, se produjo una preparación de membrana por métodos convencionales, se prepararon alícuotas en Tris-HCl 10 mM; EDTA 0,3 mM; EGTA 1 mM; sacarosa 250 mM pH 7,5 y se almacenó a -80ºC.

Las sustancias se preincubaron con la membrana a temperatura ambiente durante 15 minutos y después se añadió el radioligando (ALA-(para-F-Phe)-Arg-ChA-homoArg-(3,4-^{3}H-Tyr)-NH_2; aprox. 40 Ci/mMol).La concentración final del radioligando en el tampón de ensayo (Tris-HCl 50 mM; MgCl2 10 mM; EGTA 1 mM; BSA al 0,1%;DMSO al 2%) fue 20 nM, y la de la membrana 1 mg/ml. Después de un periodo de incubación de 60 minutos, se transfirieron 25 µl de la mezcla a una placa de filtración de microtitulación MultiScreenHTS FB de 96 pocillos (de Millipore), que se había pretratado de antemano con una solución acuosa de polietilenimina al 0,75% durante 5 horas a temperatura ambiente. Después, con extracción al vacío, cada pocillo se lavó cuatro veces con 300 µl de tampón (Tris-HCl 50 mM; MgCl2 10 mM; EGTA 1 mM). La placa después se secó durante una noche, se añadieron 100 µl de líquido de centelleo por pocillo y la placa se analizó después de 6 horas en un contador de centelleo de líquidos Wallac MicroBeta (de PerkinElmer). La unión no específica se determinó en presencia de SCH79797 100 µM (agonista de PAR-1; de Tocris, Nº de Cat. 1592) y se restó de todas las mediciones. El valor de 100% usado fue un control sin inhibidor. Los valores de inhibición en % de una serie de dilución de sustancia se usaron para calcular el valor de CI_{50} con la ayuda de un análisis de regresión no lineal de acuerdo con la ecuación de 4 parámetros.

La Tabla 2 muestra los resultados.

Tabla 2:

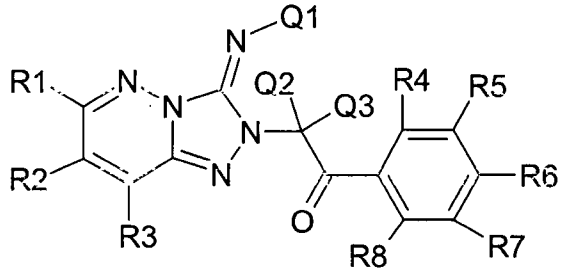
Compuesto del ejemplo	Inhibición de la unión CI_{50} [micro M]	Compuesto del ejemplo	Inhibición de la unión CI_{50} [micro M]
14	0,279	178	0,126
26	1,1	186	0,119
50	0,631	197	0,149
56	24	199	0,206
76	0,951	207	0,174
84	9,8	215	0,219
89	0,107	221	0,155
101	1,4	222	0,416
117	0,098	230	0,234
127	2,5	236	1,4
144	0,827		

161	0,365		
163	0,364		
168	0,257		
174	0,183		

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REIVINDICACIONES

1. Un compuesto de la fórmula I



(I)

y/o cualquier forma estereoisomérica o tautomérica del compuesto de la fórmula I y/o mezclas de estas formas en cualquier proporción, y/o una sal fisiológicamente compatible del compuesto de la fórmula I, en la que

Q1 es un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde cada uno de alquilo y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

Q2 y Q3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6) o -cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

R1, R2 y R3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -O-alquilo (C_1-C_8), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-C(O)-N(R11)-R12, -alquileno (C_0-C_4)-C(O)-O-R11, -alquileno (C_0-C_4)-C(O)-R11, -alquileno (C_0-C_4)-N(R11)-R12, -alquileno (C_0-C_4)-N(R11)-C(O)-R12, halógeno, OH, -CN, -NO_2, -SO_2CH_3, -SO_2CF_3, -SF_5, -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}), donde Het está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6) o -O-alquileno (C_1-C_6)-O-alquileno (C_1-C_6)-

O-alquilo (C_1-C_6), donde cada uno del alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o

-O-cicloalquilo (C_3-C_6), o

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R1 y R2 o R2 y R3, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

cada uno de R11 y R12 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), $-SO_2CH_3$ o $-SO_2CF_3$,

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R11 y R12 en los fragmentos "N(R11)-R12" y "N(R11)-C(O)-R12" representan un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-C(O)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S, donde el anillo está sin sustituir o mono- o disustituido

independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

R4, R5, R6, R7 y R8 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), OH, -CN, -NO_2, -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-(CO)-N(R21)-R22, -SO_2CH_3, -SO_2CF_3, -alquileno (C_0-C_4)-C(O)-O-R21, halógeno, -SF_5, -alquileno (C_0-C_4)-C(O)-R21, -alquileno (C_0-C_4)-N(R21)-R22, -alquileno (C_0-C_4)-N(R21)-C(O)-R22, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -alquileno (C_0-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_0-C_6)-O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -alquileno (C_0-C_6)-O-alquileno (C_0-C_6)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), o -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6),

donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-(C_3-C_6)-cicloalquilo,

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R4 y R5, R5 y R6, R6 y R7 o R7 y R8, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-

cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

cada uno de R21 y R22 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), $-SO_2CH_3$ o $-SO_2CF_3$, donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R21 y R22 en los fragmentos "N(R21)-R22" y "N(R21)-C(O)-R22" representan un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-C(O)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor.

2. Un compuesto de fórmula I según la reivindicación 1, en el que

Q1, Q2 y Q3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6) o -cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

R1, R2 y R3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-C(O)-N(R11)-R12, -alquileno (C_0-C_4)-C(O)-O-R11, -alquileno (C_0-C_4)-C(O)-R11, -alquileno (C_0-C_4)-N(R11)-R12, -alquileno (C_0-C_4)-N(R11)-C(O)-R12, halógeno, OH, -CN, $-NO_2$, $-SO_2CH_3$, $-SO_2CF_3$, $-SF_5$, -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido

independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}), donde Het está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-alquileno (C_1-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6),

donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-cicloalquilo (C_3-C_6), o

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor,

con la condición de que al menos un R1, R2 o R3 no sea un átomo de hidrógeno o

R1 y R2 o R2 y R3, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el anillo de 5 a 8 miembros, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

cada uno de R11 y R12 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), $-SO_2CH_3$ o $-SO_2CF_3$,

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R11 y R12 en los fragmentos "N(R11)-R12" y "N(R11)-C(O)-R12" representan un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-(CO)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

R4, R5, R6, R7 y R8 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), OH, -CN, -NO_2, -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-(CO)-N(R21)-R22, -SO_2CH_3, -SO_2CF_3, -alquileno (C_0-C_4)-C(O)-O-R21, halógeno, -SF_5, -alquileno (C_0-C_4)-C(O)-R21, -alquileno (C_0-C_4)-N(R21)-R22, -alquileno (C_0-C_4)-N(R21)-C(O)-R22, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -alquileno (C_0-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_0-C_6)-O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -alquileno (C_0-C_6)-O-alquileno (C_0-C_6)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), o -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6),

donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-cicloalquilo (C_3-C_6), o

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor,

con la condición de que al menos un R4, R5, R6, R7 o R8 no sea un átomo de hidrógeno, o

R4 y R5, R5 y R6, R6 y R7 o R7 y R8, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros, donde el anillo consiste únicamente en átomos de carbono o 1, 2 ó 3 de estos átomos se reemplazan por átomos de nitrógeno, oxígeno o azufre, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor,

cada uno de R21 y R22 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di- o trisustituido independientemente con -O-alquilo (C_1-C_6), -alquilo (C_1-C_4), OH, -cicloalquilo (C_3-C_6) o -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), $-SO_2CH_3$ o $-SO_2CF_3$, donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R21 y R22 en los fragmentos "N(R21)-R22" y "N(R21)-C(O)-R22" representan un anillo de 5 a 8 miembros que se forma junto con el átomo de nitrógeno "N" o el grupo "N-C(O)" para formar aminas cíclicas, imidas o lactamas que contienen hasta 2 heteroátomos adicionales del grupo de N, O y S, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno del anillo de 5 a 8 miembros formado, y en el alquilo o cicloalquilo, pueden reemplazarse por flúor.

3. Un compuesto de fórmula I de acuerdo con las reivindicaciones 1 ó 2, en el que

Q1, Q2 y Q3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6) o -cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden

reemplazarse por flúor,

R1, R2 y R3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -O-alquilo (C_1-C_8), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-C(O)-N(R11)-R12, -alquileno (C_0-C_4)-C(O)-O-R11, -alquileno (C_0-C_4)-C(O)-R11, -alquileno (C_0-C_4)-N(R11)-R12, -alquileno (C_0-C_4)-N(R11)-C(O)-R12, halógeno, OH, -CN, -NO_2, -SO_2CH_3, -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquileno (C_0-C_4)-arilo (C_6-C_{14}), -O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) o -O-alquileno (C_1-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6),

donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor,

con la condición de que al menos un R1, R2 o R3 no sea un átomo de hidrógeno o

R1 y R2 o R2 y R3, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo seleccionado entre el grupo de 2,3,5,6,7,8-hexahidro-1,2,3a,4,5,8-hexaaza-ciclopenta[b]naftaleno; 2,6,7,8-tetrahidro-3H-5-oxa-1,2,3a,4,8-pentaaza-ciclopenta[b]naftaleno; 2,3,6,7-tetrahidro-5,8-dioxa-1,2,3a,4-tetraaza-ciclopenta[b]naftaleno; 2,3,6,7-tetrahidro-5H-8-oxa-1,2,3a,4,5-pentaaza-ciclopenta[b]naftaleno; 2,6,7,8-tetrahidro-3H-5-tia-1,2,3a,4,8-pentaaza-ciclopenta[b]naftaleno; 2,3,6,7,8,9-hexahidro-1,2,3a,4,6,9-hexaazaciclopenta[a]naftaleno; 2,3-dihidro-5,7-dioxa-1,2,3a,4-tetraaza-s-indaceno; 2,6,7,8-tetrahidro-3H-ciclopenta[e][1,2,4]triazolo[4,3-b]piridazina; 2,7,8,9-tetrahidro-3H-ciclopenta[d][1,2,4]triazolo[4,3-b]piridazina y 2,3,6a,9a-tetrahidro-[1,3]dioxolo[4,5-d][1,2,4]triazolo[4,3-b]piridazina, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

cada uno de R11 y R12 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}), -alquileno (C_0-C_4)-Het (C_4-C_{15}), -SO_2CH_3 o -SO_2CF_3,

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R11 y R12 en los fragmentos "N(R11)-R12" y "N(R11)-C(O)-R12" representan un anillo de 5 a 8 miembros seleccionado entre el grupo de azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, azepinilo, morfolinilo, tiomorfolinilo, pirrolidina-2,5-dionilo, piperidina-2,6-dionilo, piperazina-2,6-dionilo, morfolina-3,5-dionilo, pirrolidin-2-onilo, piperidin-2-onilo, piperazin-2-onilo y morfolin-3-onilo, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6) donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

R4, R5, R6, R7 y R8 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), OH, -CN, -NO_2, -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-(CO)-N(R21)-R22, -SO_2CH_3, -SO_2CF_3, -alquileno (C_0-C_4)-C(O)-O-R21, halógeno, -SF_5, -alquileno (C_0-C_4)-C(O)-R21, -alquileno (C_0-C_4)-N(R21)-R22, -alquileno (C_0-C_4)-N(R21)-C(O)-R22, -alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -alquileno (C_0-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -Si[alquilo (C_1-C_4)]$_3$, -alquileno (C_0-C_6)-O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6), -alquileno (C_0-C_6)-O-alquileno (C_0-C_6)-arilo (C_6-C_{14}) o -Het (C_4-C_{15}),

donde cada uno de alquilo, alquileno y cicloalquilo está sin sustituir o mono-, di- o trisustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6), -arilo (C_6-C_{14}) donde el arilo está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), -Het (C_4-C_{15}) donde Het está sin sustituir o mono-, di-, tri-, tetra- o pentasustituido independientemente con halógeno, -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), o -O-cicloalquilo (C_3-C_6), o

donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor,

con la condición de que al menos un R4, R5, R6, R7 o R8 no sea un átomo de hidrógeno, o

R4 y R5, R5 y R6, R6 y R7 o R7 y R8, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de 5 a 8 miembros

seleccionado entre el grupo de 2,3-dihidrobenzo[1,4]dioxina; 3,4-dihidro-2H-benzo[1,4]oxazina; 1,2,3,4-tetrahidroquinoxalina; benzo[1,3]dioxol; 3,4-dihidro-2H-benzo[1,4]tiazina y 2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepina, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor,

cada uno de R21 y R22 es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-arilo (C_6-C_{14}), -alquileno (C_0-C_4)-Het (C_1-C_{15}), $-SO_2CH_3$ o $-SO_2CF_3$, donde algunos o todos los átomos de hidrógeno en el alquilo, alquileno o cicloalquilo pueden reemplazarse por flúor, o

R21 y R22 en los fragmentos "N(R21)-R22" y "N(R21)-C(O)-R22" representan un anillo de 5 a 8 miembros seleccionado entre el grupo de azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, azepinilo, morfolinilo, tiomorfolinilo, pirrolidina-2,5-dionilo, piperidina-2,6-dionilo, piperazina-2,6-dionilo, morfolina-3,5-dionilo, pirrolidin-2-onilo, piperidin-2-onilo, piperazin-2-onilo y morfolin-3-onilo, donde el anillo está sin sustituir o mono- o disustituido independientemente con -alquilo (C_1-C_4), -cicloalquilo (C_3-C_6), OH, -O-alquilo (C_1-C_6) o -O-cicloalquilo (C_3-C_6), donde algunos o todos los átomos de hidrógeno en el alquilo o cicloalquilo pueden reemplazarse por flúor.

4. Un compuesto de la fórmula I de acuerdo con las reivindicaciones 1 a 3, en el que:

Q1, Q2 y Q3 son iguales y cada uno es un átomo de hidrógeno,

R1, R2 y R3 son iguales o diferentes y cada uno es independientemente un átomo de hidrógeno, -alquilo (C_1-C_6), -O-alquilo (C_1-C_6), -O-cicloalquilo (C_3-C_6), -alquileno (C_0-C_4)-C(O)-N(R11)-R12, -alquileno (C_0-C_4)-N(R11)-R12, halógeno, -O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -O-alquilenofenilo (C_0-C_4) o -O-alquileno (C_1-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6),

donde el alquilo o alquileno, en cada caso, está sin sustituir o mono- o disustituido con -O-alquilo (C_1-C_6),

donde algunos o todos los átomos de hidrógeno en el alquilo o alquileno pueden reemplazarse por flúor,

con la condición de que al menos un R1, R2 o R3 no sea un átomo de

hidrógeno,

cada uno de R11 y R12 es independientemente un átomo de hidrógeno o -alquilo (C_1-C_6), o

R11 y R12 en el fragmento "N(R11)-R12" es un anillo de 5 a 8 miembros seleccionado entre el grupo de azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, azepinilo, imidazolilo, morfolinilo, tiomorfolinilo, pirrolidina-2,5-dionilo, piperidina-2,6-dionilo, piperazina-2,6-dionilo, morfolina-3,5-dionilo, pirrolidin-2-onilo, piperidin-2-onilo, piperazin-2-onilo y morfolin-3-onilo,

R4, R5, R6, R7 y R8 son iguales o diferentes y cada uno es independientemente

un átomo de hidrógeno, -alquilo (C_1-C_6), OH, -O-alquilo (C_1-C_8), halógeno, -SF_5, -alquileno (C_0-C_3)-N(R21)-R22, -alquileno (C_0-C_3)-N(R21)-C(O)-R22, -CF_3, -alquileno (C_0-C_6)-O-alquileno (C_1-C_6)-O-alquilo (C_1-C_6), -alquileno (C_0-C_6)-O-alquileno (C_1-C_4)-cicloalquilo (C_3-C_6) o -alquileno (C_0-C_6)-O-alquilenofenilo (C_0-C_6),

donde el alquilo o alquileno, en cada caso, está sin sustituir o mono- o disustituido con -O-alquilo (C_1-C_6),

con la condición de que al menos un R4, R5, R6, R7 o R8 no sea un átomo de hidrógeno, o

R4 y R5, R5 y R6, R6 o R7 o R7 y R8, junto con los átomos del anillo a los que cada uno de ellos está unido, forman un anillo de cinco a ocho miembros seleccionado entre el grupo de 2,3-dihidrobenzo[1,4]dioxina; 3,4-dihidro-2H-benzo[1,4]oxazina; 1,2,3,4-tetrahidro-quinoxalina; benzo[1,3]dioxol; 3,4-dihidro-2H-benzo[1,4]tiazina y 2,3,4,5-tetrahidro-1H-benzo[b][1,4]diazepina,

donde el anillo está sin sustituir o mono- o disustituido con -alquilo (C_1-C_4),

cada uno de R21 y R22 es independientemente un átomo de hidrógeno o -alquilo (C_1-C_6), o

R21 y R22 en el fragmento "N(R21)-R22" representan un anillo de 5 a 8 miembros seleccionado entre el grupo de azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, azepinilo, imidazolilo, morfolinilo, tiomorfolinilo, pirrolidina-2,5-dionilo, piperidina-2,6-dionilo, piperazina-2,6-dionilo, morfolina-3,5-dionilo, pirrolidin-2-onilo, piperidin-2-onilo, piperazin-2-onilo y morfolin-3-onilo.

5. Un compuesto de la fórmula I de acuerdo con las reivindicaciones 1 a 4, en

el que el compuesto de la fórmula I se selecciona entre el grupo de 2-(6-cloro-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(3,5-di-terc-butil-4-hidroxifenil)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-isopropoxi-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-metoxi-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(4-metoxi-3-morfolin-4-il-5-trifluoro-metilfenil)etanona, N-[3-[2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)acetil]-5-(pentafluorosulfanil)fenil]-N-metilacetamida, N-[3-[2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)acetil]-5-(pentafluorosulfanil)fenil]acetamida, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclopentiloxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclobutoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-fenoxi-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 2-(6-benciloxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclohexiloxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[3-imino-6-(2,2,2-trifluoroetoxi)-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-ciclopropilmetoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metilamino-5-(pentafluorosulfanil)fenil]etanona, 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona, 1-(3-terc-butil-5-etoximetilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-5-ciclopropilmetoxi-metilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-4,5-dietoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-5-etoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-5-propoximetilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-4,5-bis(ciclopropilmetoxi)fenil)-2-[6-(1-

etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(3-metoxi-5-trifluorometilfenil)etanona, 1-(3-terc-butil-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-5-ciclopropilmetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-5-ciclobutil-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-benciloximetil-5-terc-butilfenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-ciclo-hexilmetoxi-4,5-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 2-(6-butoxi-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-(3-terc-butil-5-metoxi-metilfenil)etanona, 1-(3-cloro-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(8-terc-butil-4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-6-il)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-piperidin-1-il-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-dietilamino-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(3-isopropil-5-metoxifenil)etanona, 1-(3-ciclohexil-metoxi-5-etoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-bromo-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-[3-(3,3-dimetilbutoxi)-5-metoxifenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-[3-(3,3-dimetilbutoxi)-5-etoxifenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-ciclohexilmetoxi-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-bromo-4,5-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 2-(6-dietilamino-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(3-imino-6-morfolin-4-il-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-imidazol-1-il-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-(5-bromo-2,3-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-

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b]piridazin-2-il]etanona, 1-(3-terc-butil-5-metoxifenil)-2-{3-imino-6-[2-(2-metoxi-etoxi)etoxi]-[1,2,4]triazolo[4,3-b]piridazin-2-il}etanona, 1-(3-cloro-4,5-dimetoxifenil)-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-dietilamino-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-[3-terc-butil-5-(2-metoxietoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-5-metoxifenil)-2-[3-imino-6-(2-metoxi-etoxi)-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-5-metoxi-metilfenil)-2-[3-imino-6-(2-metoxietoxi)-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-morfolin-4-il-5-(pentafluorosulfanil)fenil]etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-(5-metoxi-3-pentafluorosulfanilfenil)etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-3-imino-[1,2,4]triazolo[4,3-b]-piridazin-2-il)etanona, 1-[3-terc-butil-5-(2-metoxietoxi-metil)fenil]-2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-(2-metoxietoxi)-5-(pentafluorosulfanil)fenil]etanona, 2-(6-etoxi-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil) fenil]etanona, 2-[6-(1-etilpropoxi)-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il]-1-[3-(3-metoxipropoxi)-5-(pentafluorosulfanil)fenil]etanona, N,N-dietil-2-[2-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-oxoetil]-6-cloro-3-imino-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida, N,N-dietil-6-cloro-3-imino-2-{2-[3-metoxi-5-(pentafluorosulfanil)fenil]-2-oxoetil}-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-8-carboxamida, 2-(6-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-etil-3-imino-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, 1-[3-terc-butil-5-(3-metoxipropoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-[3-terc-butil-5-(2-metoxietoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-5-ciclopropilmetoxi-fenil)-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 1-(3-terc-butil-5-metoxifenil)-2-[6-(1-etilpropoxi)-3-imino-8-metil-[1,2,4]triazolo[4,3-

b]piridazin-2-il]etanona, 1-[3-terc-butil-5-(3-metoxipropoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona, 2-(6-cloro-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)-1-[3-metoxi-5-(pentafluorosulfanil)fenil]etanona, 1-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-(6-cloro-3-imino-7,8-dimetil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona, N,N-dietil-6-cloro-3-imino-2-{2-[3-metoxi-5-(pentafluorosulfanil)-fenil]-2-oxoetil}-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida, N,N-dietil-2-[2-(3-terc-butil-4-metoxi-5-morfolin-4-ilfenil)-2-oxoetil]-6-cloro-3-imino-2,3-dihidro-[1,2,4]triazolo[4,3-b]piridazina-7-carboxamida, 1-[3-terc-butil-5-(3-metoxipropoxi)fenil]-2-(6-etoxi-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il)etanona o 1-[3-terc-butil-5-(2-metoxietoxi)fenil]-2-[6-(1-etilpropoxi)-3-imino-7-metil-[1,2,4]triazolo[4,3-b]piridazin-2-il]etanona.

6. Un medicamento, caracterizado por un contenido eficaz de al menos un compuesto de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 5 junto con un vehículo, aditivo y/u otros ingredientes activos y excipientes farmacéuticamente adecuados y fisiológicamente compatibles.

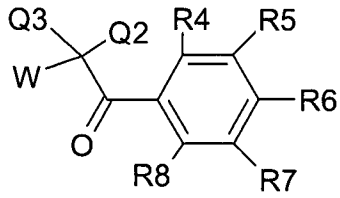
7. El uso del compuesto de la fórmula I de acuerdo con una o más de las reivindicaciones 1 a 5 para uso en un método para la profilaxis, prevención secundaria y tratamiento de todos los trastornos asociados con trombosis, embolia, hipercoagulabilidad, cambios fibróticos o trastornos inflamatorios.

8. El uso de acuerdo con la reivindicación 7 que se aplica a infarto de miocardio, angina de pecho y otras formas de síndrome coronario agudo, apoplejía, trastornos vasculares periféricos, trombosis de venas profundas, embolia pulmonar, acontecimientos embólicos o trombóticos provocados por arritmias cardíacas, acontecimientos cardiovasculares tales como reestenosis después de una revascularización y angioplastia y procedimientos similares tales como implantes de endoprótesis vasculares y operaciones de derivación vascular, o la reducción del riesgo de trombosis después de procedimientos quirúrgicos tales como operaciones de articulaciones de rodilla y de cadera, o procedimientos que conducen al contacto de la sangre con superficies extrañas, tal como para pacientes de diálisis y pacientes que tienen catéteres permanentes o coagulación

intravascular diseminada, sepsis y otros acontecimientos intravasculares acompañados de inflamación, aterosclerosis, diabetes y el síndrome metabólico y sus secuelas, crecimiento tumoral y metástasis tumoral, trastornos inflamatorios y degenerativos de las articulaciones tales como artritis reumatoide y artrosis, alteraciones del sistema hemostático tales como depósitos de fibrina, cambios fibróticos del pulmón, tales como enfermedad pulmonar obstructiva crónica, síndrome de insuficiencia respiratoria del adulto o depósitos de fibrina en el ojo después de operaciones oculares o prevención y/o tratamiento de la formación de cicatrices.

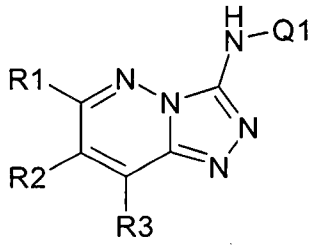
9. Un procedimiento para preparar el compuesto de la fórmula I, de acuerdo con una o más de las reivindicaciones 1 a 5, que comprende

a) hacer reaccionar un compuesto de la fórmula II



(II)

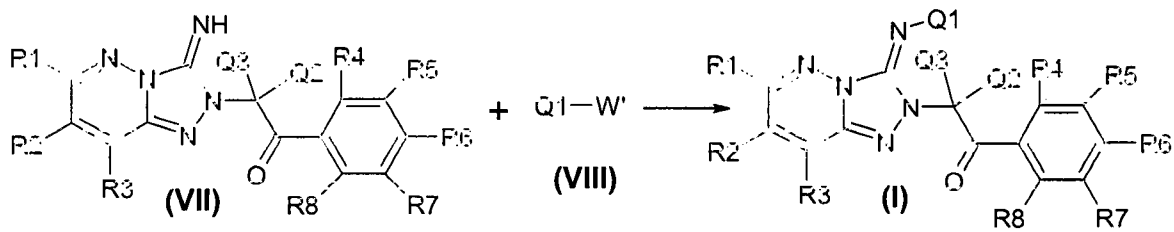
en la que cada uno de R4 a R8, Q2 y Q3 es como se ha definido en la fórmula I y W es cloruro, bromuro, mesilato o tosilato con un compuesto de la fórmula III



(III)

en la que cada uno de R1, R2, R3 y Q1 es como se ha definido en la fórmula I, con o sin la adición de una base, en un disolvente para dar un compuesto de la fórmula I, o

b) hacer reaccionar un compuesto de la fórmula VII



en la que cada uno de R1, R2, R3, R4, R5, R6, R7, R8, Q1, Q2 y Q3 es como se ha definido en la fórmula I con un compuesto Q-W' en el que W' es cloruro, bromuro, mesilato, tosilato, metilsulfato o un grupo saliente adecuado similar, con o sin la adición de una base, para dar un compuesto de la fórmula I, o

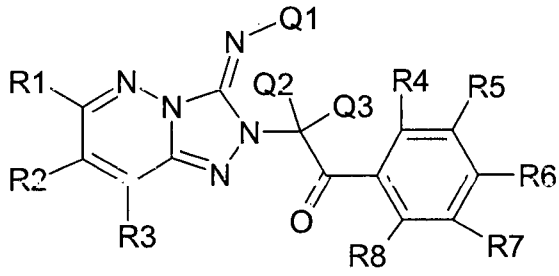
c) aislar el compuesto de la fórmula I preparado por el método a) o b) en forma libre o liberarlo de sales fisiológicamente incompatibles o, en el caso de que haya presencia de grupos ácidos o básicos, convertirlo en sales fisiológicamente compatibles, o

d) separar un compuesto de la fórmula I preparado por el método a) o b), o un precursor adecuado de la fórmula I que, debido a su estructura química, se da en formas enantioméricas o diastereoméricas, en los enantiómeros o diastereómeros puros por formación de sal con ácidos o bases enantioméricamente puras, cromatografía sobre fases estacionarias quirales o derivatización por medio de compuestos enantioméricamente puros quirales tales como aminoácidos, separación de los diastereómeros obtenidos de esa manera y eliminación de los grupos auxiliares quirales.

Resumen

TRIAZOLOPIRIDAZINAS COMO INHIBIDORES DE PAR1, SU PREPARACIÓN Y USO COMO MEDICAMENTOS

La invención se refiere a compuestos de fórmula (I)



(I)

con actividad antitrombótica, que inhiben especialmente el receptor 1 activado por proteasa, a métodos para su preparación y a su uso como medicamentos.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

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PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional :

(71)Solicitante(s) **SANOFI-AVENTIS**

(72) Inventor(es) **UWE HEINELT, VOLKMAR WEHNER, MATTHIAS HERRMANN, KARL SCHOENAFINGER, HENNING STEINHAGEN, BODO SCHEIPER**

(74) Apoderado: **DR. LUIS PATIÑO LEYVA**

(30) Prioridad	(31) Nº Prioridad	(32) Fecha	(33) País
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Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISION A TRAMITE - NUEVAS CREACIONES

PATENTE DE INVENCION [ ] **MODELO DE UTILIDAD** [ ] **Art. 33 Decisión 486/00**

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

Completa [ ] Incompleta [ ]

PATENTE DE INVENCION PCT [X] **MODELO DE UTILIDAD PCT** [ ] **Art. 33 Decisión 486/00 Circular Única**

- [X] Indicación que se solicita una PCT
- [X] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [X] Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- [ ] Dibujos de ser estos pertinentes
- [X] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [X] Incompleta [ ]

DISEÑO INDUSTRIAL [ ] **(Art. 119 Decisión 486/00)**

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

Completa [ ] Incompleta [ ]

ESQUEMA DE TRAZADO [ ] **(Art. 92 Decisión 486/00)**

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

Completa [ ] Incompleta [ ]