Organizacion y Digitalizacion CSA Ltda
CSA125941
Organizacion y Digitalizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

PCT

Delegatura de Propie
División de Nuevas

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-121065- -00000-0000
Fecha: 2010-09-30 11:37:47 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 723

SOLICITUD

PATENTE DE INVENCIÓN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

21. **EXPEDIENTE No.** 10-121065

1/3

54. **TÍTULO** DERIVADOS DE 1-HETEROCICLICO-1,5-DIHIDRO-PIRAZOLO[3,4-D] PIRIMIDIN-4-ONA Y SU USO COMOMODULADORES DE LA PDE9A

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** BOEHRINGER INGELHEIM INTERNATIONAL GMBH

DOMICILIO INGELHEIM AM RHEIN, ALEMANIA

74. **APODERADO** LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén

22. **BOGOTÁ, D.C.,**

(FORMA P-10)

Recibo no Conforme
02-11-2010

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-121065- -00000-0000
Fecha: 2010-09-30 11:37:47 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 723

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:

1. ☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
   ☒ Capítulo I. ☐ Capítulo II.

2. SOLICITANTE (71)

Nombre: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
Sociedad constituida y existente bajo las leyes de Alemania.

Dirección: Binger Strasse 173,
55216 Ingelheim am Rhein,
Alemania

Domicilio: Ingelheim am Rhein,
Alemania

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3. REPRESENTANTE O APODERADO

Nombre: LUZ CLEMENCIA DE PAEZ
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 35.456.344 T.P 23.555

4. INVENTOR (ES) (72)

1. **Riccardo GIOVANNINI**
   Boehringer Ingelheim GmbH,
   CD Patents,
   Binger Strasse 173,
   55216 Ingelheim am Rhein,
   Alemania

2. **Cornelia DORNER-CIOSSEK**
   Boehringer Ingelheim GmbH,
   CD Patents,
   Binger Strasse 173,
   55216 Ingelheim am Rhein,
   Alemania

3. **Christian EICKMEIER**
   Boehringer Ingelheim GmbH,
   CD Patents,
   Binger Strasse 173,
   55216 Ingelheim am Rhein,
   Alemania

4. **Dennnis FIEGEN**
   Boehringer Ingelheim GmbH,
   CD Patents,
   Binger Strasse 173,
   55216 Ingelheim am Rhein,
   Alemania

5. **Thomas FOX**
   Boehringer Ingelheim GmbH,
   CD Patents,
   Binger Strasse 173,
   55216 Ingelheim am Rhein,
   Alemania

6. **Klaus FUCHS**
   Boehringer Ingelheim GmbH,
   CD Patents,
   Binger Strasse 173,
   55216 Ingelheim am Rhein,
   Alemania

7. **Niklas HEINE**
   Boehringer Ingelheim GmbH,
   CD Patents,
   Binger Strasse 173,
   55216 Ingelheim am Rhein,
   Alemania

8. **Holger ROSENBROCK**
   Boehringer Ingelheim GmbH,
   CD Patents,
   Binger Strasse 173,
   55216 Ingelheim am Rhein,
   Alemania

9. **Gerhard SCHAENZLE**
   Boehringer Ingelheim GmbH,
   CD Patents,
   Binger Strasse 173,
   55216 Ingelheim am Rhein,
   Alemania

5 **PCT (86)**
Solicitud Internacional No. PCT/EP2009/053907 Fecha: 1 de abril de 2009
Publicación Internacional No. WO 2009/121919 A1 Fecha: 8 de octubre de 2009

6 **Título (54)**
DERIVADOS DE 1-HETEROCICLILO-1,5-DIHIDRO-PIRAZOLO[3,4-D]PIRIMIDIN-4-ONA Y SU USO COMO MODULADORES DE LA PDE9A

7 **Clasificación Internacional (51)** C07D 487/004

8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	EP	2 de abril de 2008	08153987.6

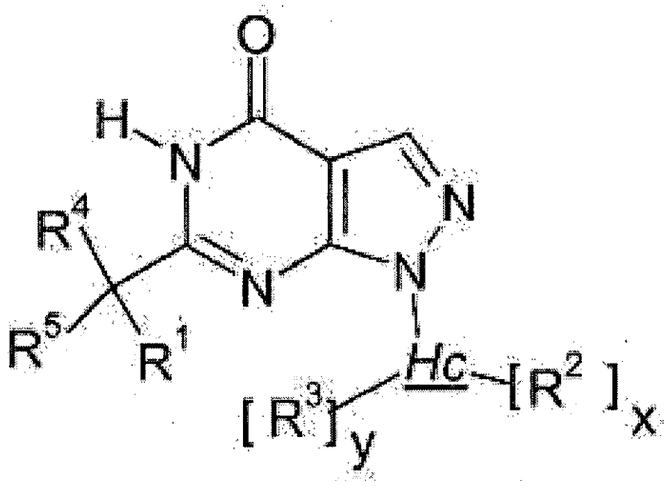
9 **Comprobante de pago No.:** 10-75,733 **Fecha:** 13 de septiembre de 2010
Comprobante de pago No.: 10-78,499 **Fecha:** 13 de septiembre de 2010

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 554.000.oo.
- ☒ Comprobante de pago por 18 reivindicaciones adicionales después de la décima reivindicación por $468.000.oo.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 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.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



(I)

12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PAEZ

FIRMA : Luz Clemencia de Páez

C.C. 35.456.344 de Usaquén T.P. 23.555

JGG

4

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2009/121919 A1

   Descripción:

   Páginas 274 en el idioma original

   Páginas 283 en español

   Reivindicaciones: Número (s) 28

   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

CONSULADO GENERAL DE COLOMBIA

MUNICH

Nr. 169

El Cónsul General de Colombia

C E R T I F I C A

Que el Dr. Hanns Paul Tüttenberg -----, quién autentica la firma del signatario en el presente documento, ejercía en la fecha alli indicada las funciones de Presidente del Tribunal Regional -en Mainz. ----------

Que la firma BOEHRINGER INGELHEIM INTERNATIONAL GmbH, domiciliada en 55216 Ingelheim am Rhein, Registro Mercantil Nr. HR B 1063 del Juzgado Municipal de Bingen ---------- está constituída y ejerce su objeto social de conformidad con las leyes de la República Federal de Alemania.

Que los señores Dr. DIETER LAUDIN Y Dr. GERHARD HUBER ----------

quien (es) firman el presente documento tiene (n) facultad legal suficiente para representar a la mencionada firma y otorgar poderes en su nombre.

Que ha tenido a la vista la documentación que prueba lo anterior.

Munich, 18 de Diciembre de 1995

CONSULADO GENERAL DE COLOMBIA * MUNICH *

RICARDO MOSQUERA MESA
CONSUL GENERAL DE COLOMBIA

Derechos para la Nación	US $	6.-
Fondo Rotatorio	US $	100.-
Tasa consular	US $	1 x DM 1,60 = DM 169.60

PAGADO

28 SEP 2010

NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

CONSULADO GENERAL DE COLOMBIA * MUNICH *

MINISTERIO DE RELACIONES EXTERIORES

NO SE ASUME RESPONSABILIDAD DEL TEXTO

1440 ENE -4 A 11:44

JEFE DE LEGALIZACIONES
CANTAFE DE BOGOTA D.C.

DOCUMENTO DESPACHADO
LAS FUNCIONES INDICADAS

28 SEP 2010

NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

COLOMBIA

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

9255
0569

I (we), the undersigned/Yo (nosotros), abajo firmado (s)
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

of/domiciliado (s) en D-55216 Ingelheim am Rhein, GERMANY

por el presente nombramos a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; y LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciliados en la Carrera 4ª Nº 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; and LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciled at Carrera 4ª Nº 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement [illegible] the action for writ mandamus, [illegible] general the civil, penal, [illegible] those rights; actions and [illegible] substituted by me (us) [illegible] me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Ingelheim am Rhein, 26 SET 2000 12.1995

NOTARIO ENCARGADO

Given and signed this/Dado y firmado hoy _____

BOEHRINGER INGELHEIM
in/en INTERNATIONAL GMBH

ppa. Dr. Dieter Laudien
Signature

ppa. Dr. Gerhard Hube
Firma

REPÚBLICA DE COLOMBIA
Jaime Vargas
NOTARIO
NOTARÍA SEXTA DE BOGOTÁ

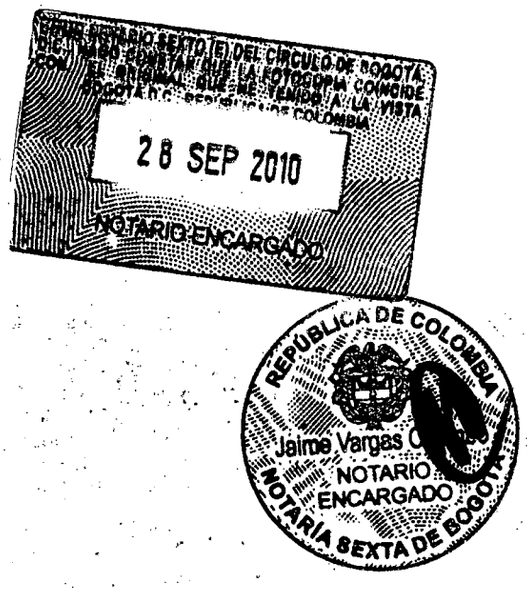
© CAVELIER ABOGADOS

LEGALIZACION

El Señor Cónsul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a *consular* the legal existence of the company whic Power-of-Attorney, (2) that it is in actual ex company purposes, and (3) that the persons who Power of Attorney is autorized to do so. To this effec show the Consul the evidence to prove the above facts and (3).



NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.

Ur.-Nr. 2659 / 95 V

Vorseitige, vor mir gefertigte Namensunterschriften der Herren:

1. Dr. Dieter L a u d i e n, Dipl.-Chemiker, wohnhaft in 55127 Mainz,.

2. Dr. Gerhard H u b e r, Rechtsanwalt, wohnhaft in 55411 Bingen,

- mir bekannt -

beglaubige ich hiermit.

Gleichzeitig bescheinige ich aufgrund heutiger Einsichtnahme in das Handelsregister des Amtsgerichts Bingen, daß die Firma Boehringer Ingelheim International GmbH mit Sitz in Ingelheim am Rhein im Handelsregister des Amtsgerichts Bingen unter HR B 1063 eingetragen ist und daß die Herren Dr. Laudien und Dr. Huber als Prokuristen gemeinschaftlich zur Vertretung der Gesellschaft berechtigt sind.

Ingelheim am Rhein, den 12. Dezember 1995/hün

Notariatsverweser
anstelle des Notars
Prof. Dr. Weirich in Ingelheim

Landgericht Mainz

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PRESENTADO
28 SEP 2010
NOTARIO ENCARGADO

- 910 E 1 -

Die Echtheit vorstehender Unterschrift des Notariatsverwesers Dr. Peter Wirth - Notariatsverweser anstelle des Notars Prof. Dr. Weirich in Ingelheim und die Echtheit des beigedruckten Dienst - xxxxxxxx - siegels wird hiermit bestätigt. Zugleich wird bescheinigt, daß [illegible] zur Vornahme der Amtshandlung gesetzlich befugte

REPÚBLICA DE COLOMBIA NOTARIA SEXTA DE BOGOTA

Kostenberechnung:
Gebühr für Legalisation
(Wert: DM 5.000,-)
JVKostO. v. 26.7.1957
BGBl. I S. 861 20,-

Mainz, den dreizehnten Dezember neunzehnhundertfünfundneunzig
Der Präsident des Landgerichts

(Dr. Hanns Paul Tüttenberg)

995

Amtsinspektor

8

TRADUCCION OFICIAL No. 5133

de un documento escrito en Alemán, el cual para su identificación se sella con el sello de la traductora, lo mismo que la presente.-

---

(A continuación del poder conferido a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO tpa, 31929; y LUZ CLEMENCIA DE PAEZ, tpa 23555; domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia, por la BOEHRINGER INGELHEIM INTERNATIONAL GMBH, domiciliada en D-55216 Ingelheim am Rhein, RFA, a través de sus representantes los Srs. Dr. Dieter Laudien y Dr. Gerhard Huber:)

Legalización

Protocolo notarial No. 2659/95 V

Certifico la autenticidad de las firmas antecedentes puestas ante mí por los señores:

1. Dr. Dieter Laudien, Dipl. Chim., domiciliado en 55127 Mainz,

2. Dr. Gerhard Huber, abogado, domiciliado en 55411 Bingen

a quienes conozco en persona.

1

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. COLOMBIA
28 SEP 2010
NOTARIO ENCARGADO
REPUBLICA DE COLOMBIA
Jaime Vargas C.
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

4

Igualmente certifico, por haber examinado en la fecha el Registro de Comercio del Juzgado Municipal de Bingen, HR B 1063, que la firma Boehringen Ingelheim International GmbH, domiciliada en Ingelheim am Rhein, está inscrita bajo el No. HR B 1063 en el Registro de Comercio del Juzgado Municipal de Bingen y que los señores Dr. Laudien y Dr. Huber, en su calidad de apoderados, están facultados para representar conjuntamente a la sociedad.

Ingelheim am Rhein, 12 de diciembre de 1995/hün

Fdo.: firma ilegible

(Hilo y oblea roja en relieve:)
El notario suplente - Ingelheim

El notario suplente
del notario de Ingelheim
Prof. Dr. Weirich

(dos sellos redondos en tinta del Tribunal Regional de Mainz)

910 E 1

Se certifica la autenticidad de la firma antecedente del Dr. Peter Wirth, como notario suplente del Prof. Dr. Weirich, notario de Ingelheim, y la del sello oficial que la acompaña. Igualmente se certifica que el mencionado notario estaba facultado para realizar ese acto oficial.

Mainz, trece de diciembre de mil novecientos noventa y cinco

COMO NOTARIO SEXTO (E) DEL CÍRCULO DE BOGOTÁ D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTÁ D.C. REPÚBLICA DE COLOMBIA
28 SEP 2010
NOTARIO ENCARGADO

REPÚBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

El Presidente del Tribunal Regional

(E) Fdo.: firma ilegible

(Dr. Hanns Paul Tüttenberg)

Costas

Derechos de legalización
(Valor:DM 5.000,-)
JVKostO del 26 de julio 1957
Gacetas Oficial I Pag. 861
DM 20,--
Mainz, 13 de diciembre de 1995
Fdo.: firma ilegible
Inspector

EN ESPAÑOL: La legalización de las firmas antecedentes por el Consulado de Colombia en Munich bajo el No. 169 del 18 de diciembre de 1995, y por el Ministerio de Relaciones Exteriores de Colombia bajo el No. 051606 del 4 de enero de 1996.

Pagados derechos y Fondo Rotatorio US$ 106,--

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de estas oficinas para su confrontación.

Santafé de Bogotá, 6 de enero de 1996.

LUZ ARRIAGA DE HERNEN
TRADUCTORA E INTERPRETE OFICIAL
Resolución No. 0599 Ministerio

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, DIC. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
28 SEP 2010
NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas C.
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA HAGO CONSTAR QUE LA FIRMA DE

C. C.

COINCIDE CON LA REGISTRADA POR EL (ELLA) EN ESTA NOTARIA.

09 ENE 1996

SANTAFE DE BOGOTA D.C.

NOTARIA SEXTA
PABLO MENDEZ BARAJAS
Notario Sexto Encargado

NO SE ASUME RESPONSABILIDAD DEL TEXTO

1996 ENE 10 A 11: 33

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

001911

CUYA FIRMA A [illegible] DOCUMENTO [illegible] LAS FUNCIONES [illegible]

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA

28 SEP 2010

NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

CAVELIER
ABOGADOS

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTA 8, COLOMBIA

WEB SITE: www.cavelier.com
E-MAIL: cavelier@cavelier.com

TELEFONO: (57) (1) 347-3611
TELEFAX: (57) (1) 217-9211 (57) (1) 310-4995

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Poderdante : **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**

Poder conferido el : 12/12/1995

Yo, EMILIO FERRERO, obrando como apoderado principal del poderdante arriba mencionado, mediante el presente escrito sustituyo el poder a mi otorgado a la doctora LUZ CLEMENCIA DE PAEZ, identificada con cédula de ciudadanía No. 35.456.344 y Tarjeta Profesional N°23.555, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil.

Señora Jefe,

EMILIO FERRERO
T.P.A. N° 31.929
C.C. N° 438.019 de Usaquén

Acepto:

LUZ CLEMENCIA DE PAEZ
T.P.A. N° 23.555
C.C. No. 35.456.344 de Usaquén

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME HA SIDO PUESTO A LA VISTA
BOGOTÁ D.C. - REPÚBLICA DE COLOMBIA
28 SEP 2010
NOTARIO ENCARGADO

REPÚBLICA DE COLOMBIA
Jaime Vargas C.
NOTARIO ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

NOTARIA SEXTA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C.
Ante el 03 NOV 2009
NOTARIO SEXTO (E) DEL CIRCULO DE
BOGOTA D.C.
Compareció (eron)
Quien(es) exhibió(aron) la(s) C.C.
Y declaró(aron) que la(s) firma(s) que aparece(n)
en el presente documento es(son) la(s) suya(s) y
que el contenido del mismo es cierto.
En constancia se firma esta diligencia.

REPÚBLICA DE COLOMBIA
NOTARIA SEXTA DE BOGOTA
Jaime Vargas
NOTARIO
ENCARGADO

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA D.C. PAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
28 SEP 2010
NOTARIO ENCARGADO

REPÚBLICA DE COLOMBIA
Jaime Vargas
NOTARIO
ENCARGADO
NOTARIA SEXTA DE BOGOTA

Certified Copy

Assignment of Inventors

For good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the undersigned (the "Assignors")

Riccardo GIOVANNINI, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Italy
Cornelia DORNER-CIOSSEK, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Christian EICKMEIER, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Dennis FIEGEN, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Thomas FOX, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Klaus FUCHS, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Niklas HEINE, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Holger ROSENBROCK, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Gerhard SCHAENZLE, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany

inventor/s of an invention related to:

"NEW COMPOUNDS FOR THE TREATMENT OF CNS DISORDERS"

for which a first application was filed in **Europe**
Serial No.: **EP 08153987.6**
Filing Date: **April 2, 2008**

do hereby assign, and transfer all my/our rights, title and interest in and to the same to

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
residing in
Binger Strasse 173, 55216 Ingelheim am Rhein, Germany

to whom assignment has been made of all rights and title to the said invention for the following territories:

Argentina, Brazil, Canada, Chile, China, Colombia, Ecuador, Egypt, India, Indonesia, Pakistan, Peru, South Africa, Taiwan, Thailand, Uruguay, Venezuela, Viet Nam, GCC Member States and the United Arabian Emirates

aforesaid without any restriction whatever.
Done and signed at

Riccardo GIOVANNINI

01/04/2009
Date

EZIO RICCI NOTAIO
20121 MILANO - VIA A. APPIANI, 2 - TEL. 02 - 65[illegible]05 - FAX 02 - 654339
20097 S. DONATO MILANESE - VIA J. F. KENNEDY, 28 - TEL. [illegible]51621 - FAX 02 - 51621348

Cornelia DORNER-CIOSSEK	Date
Christian EICKMEIER	Date
Dennis FIEGEN	Date
Thomas FOX	Date
Klaus FUCHS	Date
Niklas HEINE	Date
Holger ROSENBROCK	Date
Gerhard SCHAENZLE	Date

Vera autogr
inglese a m
- **GIOVANN**
residente in
certo.
Milano, 1 (u

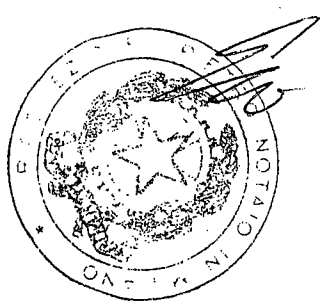
Case: P01-2:
2 c

14

Vera autografa e apposta in mia presenza la firma, sulla presente scrittura in lingua inglese a me nota dal signor:

- **GIOVANNINI Riccardo** nato a San Severino Marche (MC) il giorno 4 febbraio 1969, residente in Verona (VR), Via Lucania n. 20, della cui identità personale io Notaio sono certo.

Milano, 1 (uno) aprile 2009 (duemilanove).



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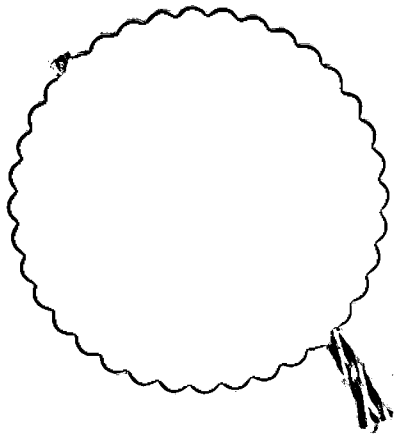
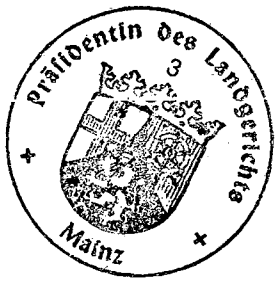
Conformity of the above copy with the original is hereby certified.

Ingelheim am Rhein, the 13th day of July 2010/Ke

Notary public





APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland

Diese öffentliche Urkunde

2. ist unterschrieben von Horst Heintskill

3. in seiner Eigenschaft als Notar

4. sie ist versehen mit dem Siegel/Stempel Horst Heintskill - Notar in Ingelheim am Rhein

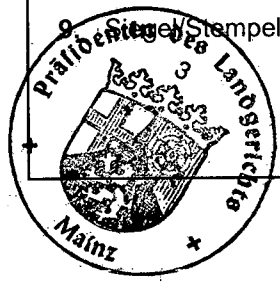
Bestätigt

5. in Mainz 6. am 15.07.2010

7. durch die Präsidentin des Landgerichts

8. unter Nr. 1280/2010

9. Siegel/Stempel



10. Unterschrift

Marliese Dicke

Kostenrechnung:

Gebühr für die Erteilung der Legalisation
Wert: 3.000,00 €
JVKostO v. 26.7.1957
i.V.m. § 45 KostO
Gebühr: 10,00 €

Mainz, den 15.07.10

Beyer
Justizbeschäftigte

Certified Copy

(AH)

CO

Assignment of Inventors

For good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the undersigned (the "Assignors")

Riccardo GIOVANNINI, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Italy
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Christian EICKMEIER, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Dennis FIEGEN, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Thomas FOX, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Klaus FUCHS, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Niklas HEINE, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Holger ROSENBROCK, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany
Gerhard SCHAENZLE, Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany, a citizen of Germany

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aforesaid without any restriction whatever.
Done and signed at

Riccardo GIOVANNINI

Date

../2

17

Cornelia DORNER-CIOSSEK — 03/17/2009 Date

Christian EICKMEIER — 03/17/2009 Date

Dennis FIEGEN — 04/01/2009 Date

Thomas FOX — 03/23/2009 Date

Klaus FUCHS — 03/23/2009 Date

Niklas HEINE — 03/23/2009 Date

Holger ROSENBROCK — 03/17/2009 Date

Gerhard SCHAENZLE — 03/23/2009 Date

Urkundenrolle I UR 192 / 2009
Notariat 1 Biberach a.d. Riß*Tel. 07351/180310*Fax 07351/180366

I UZ 199 / 2009

Notarielle Beglaubigung

Vorstehende, vor mir vollzogene Unterschrift von

1. Frau Dr. Cornelia Dorner-Ciossek geb. Dorner,
   geboren am 20.09.1970,
   wohnhaft in 88447 Warthausen, Hanns-Wanner-Weg 9,

   - ausgewiesen durch Personalausweis -

2. Herrn Dr. Christian Eickmeier,
   geboren am 08.07.1966,
   wohnhaft in 88441 Mittelbiberach, Ayestrasse 10/2,

   - ausgewiesen durch Personalausweis -

3. Herrn Dr. Dennis Fiegen,
   geboren am 11.01.1977,
   wohnhaft in 88400 Biberach, Zwingergasse 9,

   - persönlich bekannt -

4. Herrn Dr. Thomas Fox,
   geboren am 21.07.1964,
   wohnhaft in 88400 Biberach, Grüner Weg 11,

   - ausgewiesen durch Reisepass -

5. Herrn Dr. Klaus Fuchs,
   geboren am 28.03.1963,
   wohnhaft in 88441 Mittelbiberach, Klingenaecker 27,

   - ausgewiesen durch Personalausweis -

6. Herrn Dr. Niklas Heine,
   geboren am 04.08.1971,
   wohnhaft in 88400 Biberach, Georg-Schinbain-Str. 66,

   - ausgewiesen durch Personalausweis -

7. Herrn Dr. Holger Rosenbrock,
   geboren am 15.08.1969,
   wohnhaft in 88441 Mittelbiberach, Klingenäcker 14,

   - ausgewiesen durch Personalausweis -

19

8. Herrn Dr. Gerhard Schänzle,
geboren am 11.08.1967,
wohnhaft in 88400 Biberach, Sophie-von-La-Roche-Weg 10,

- persönlich bekannt -

beglaubige ich hiermit öffentlich.

Biberach a.d. Riß, den 01.04.2009

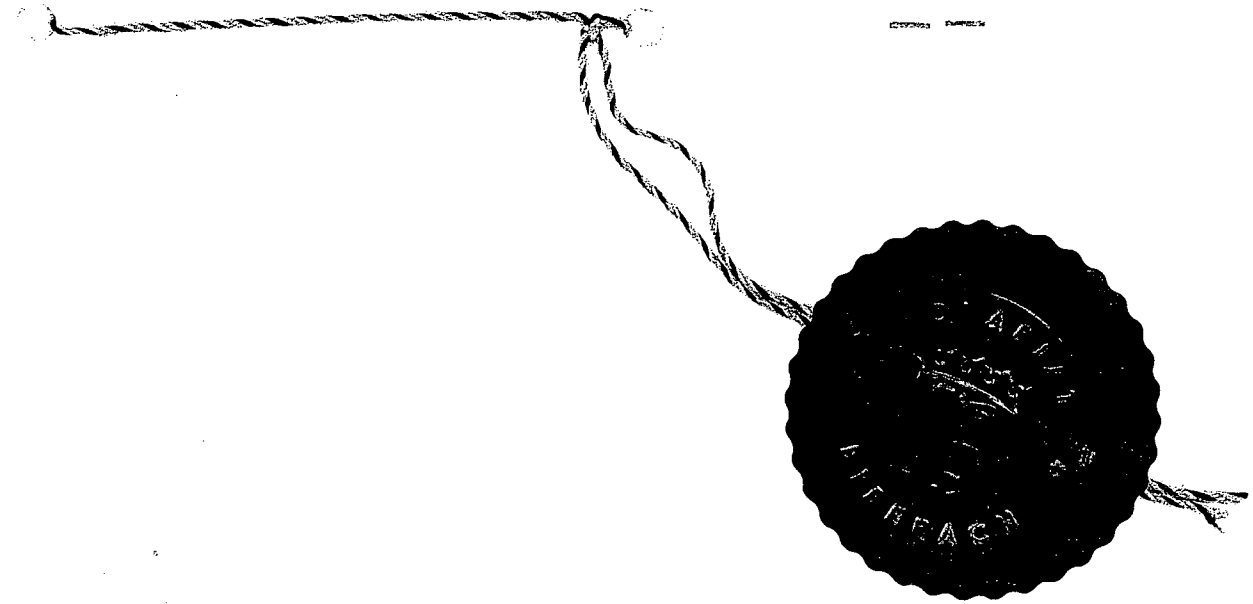
Notar

(Groß)

NOTARIAT BIBERACH AN DER RISS

§§ KostO	Gegenstand	Geschäftswert	Betrag
§§ 45 I, 141, 32 KostO	Unterschriftsbeglaubigung	50.000,00 €	33,00 €
§§ 58 I, 141, 32 KostO	Auswärtsgebühr	50.000,00 €	30,00 €
§§ 58 I, 141, 32 KostO	Auswärtsgebühr	50.000,00 €	30,00 €
§§ 58 I, 141, 32 KostO	Auswärtsgebühr	50.000,00 €	30,00 €
	Umsatzsteuer 19,00% aus	123,00 €	23,37 €
Summe:			**146,37 €**

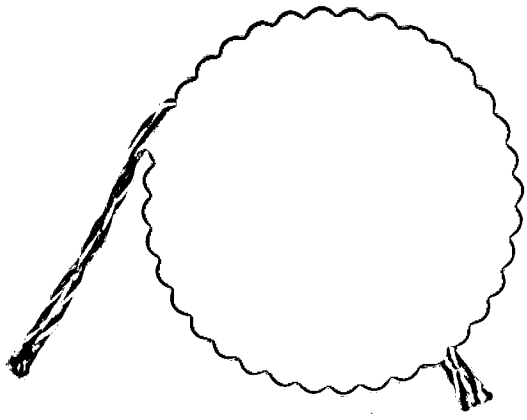
Rechnungs-Nr.: 103661



Conformity of the above copy with the original
is hereby certified.

Ingelheim am Rhein, the 13th day of July 2010/Ke

Notary public



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

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4. sie ist versehen mit dem Siegel/Stempel Horst Heintskill - Notar in Ingelheim am Rhein

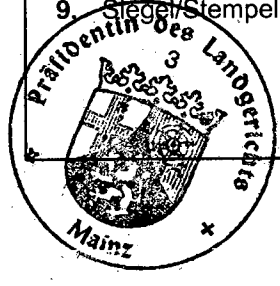
Bestätigt

5. in Mainz 6. am 15.07.2010

7. durch die Präsidentin des Landgerichts

8. unter Nr. 1279/2010

9. Siegel/Stempel



10. Unterschrift

Marliese Dicke

Kostenrechnung:

Gebühr für die Erteilung der Legalisation
Wert: 3.000,00 €
JVKostO v. 26.7.1957
i.V.m. § 45 KostO
Gebühr: 10,00 €

Mainz, den 15.07.10

Beyer
Justizbeschäftigte

SANDRA MÓNICA BARRIGA BALMA
Traductora e Intérprete Oficial
Resolución Ministerio de Justicia N° 735 del 20 de septiembre de 2001

TRADUCCIÓN OFICIAL T.O. # 06/10 COLO : 9255 841 151 5 *de una legalización de un documento redactado en idioma Inglés denominado* ***"ASIGMENT OF INVENTORS",*** *realizada el día 13 de septiembre de 2010 por SANDRA MÓNICA BARRIGA BALMA, Abogada y Traductora Oficial de Confianza de las Embajadas de Italia y Suiza en Colombia, nombrada para el cargo mediante Resolución Min-Justicia N° 735 del 20 de Septiembre de 2001.*

Se certifica como verdadera y auténtica la firma colocada en mi presencia en la presente escritura redactada en Inglés, idioma del cual tengo conocimiento, por el señor:

- **GIOVANNINI Riccardo**, nacido en San Severino Marche (MC), el día 4 de febrero de 1969, residente en verona (VR), Via Lucania N° 20, de cuya identidad personal, como Notario doy fe.

Milán, 1 (primero) de abril de 2009 (dos mil nueve).

Firmado ilegible y sellado por el Notario

La apostilla de este documento está redactada en idioma Alemán

Res. Minjusticia 735 20 de
ESPAÑOL - ITALIANO - ESPAÑOL

TRADUCCION OFICIAL 267/2010 DE UN DOCUMENTO EN IDIOMA INGLÉS REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL AUTORIZADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE COLOMBIA

CESION DE INVENTORES

A cambio de una compensación adecuada y valiosa, de la cual y de cuya suficiencia se acusa recibo por la presente, los abajo firmantes ("los cedentes"), a saber

RICARDO GIOVANNINI, BOEHRINGER INGELHEIM GMBH, CD PATENTS, DOMICILIADO EN BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, ALEMANIA, CIUDADANO DE ITALIA; CORNELIA DORNER-CIOSSEK, BOEHRINGER INGELHEIM GMBH, CD PATENTS, DOMICILIADO EN BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, ALEMANIA, CIUDADANA ALEMANA; CHRISTIAN EICKMEIER, CIUDADANO ALEMAN; DENNIS FIEGEN, CIUDADANO ALEMAN; THOMAS FOX, CIUDADANO ALEMAN; KLAUS FUCHS, CIUDADANO ALEMAN; NIKLAS HEINE, CIUDADANO ALEMAN; HOLGER ROSENBROCK, CIUDADANO ALEMAN Y GERHARD SCHAENZLE (TODOS LOS ANTERIORES DE BOHERINGER INGELHEIM GMBH, CD PATENTS Y DOMICILIADOS EN LA DIRECCIÓN ARRIBA ANOTADA)

Inventores de un invento relacionado con **"NUEVOS COMPUESTOS PARA EL TRATAMIENTO DEL SISTEMA NERVIOSO CENTRAL"**

Por el cual se presentó una primera solicitud en Europa

Número EP 08153987.6; Fecha de radicación: 2 de abril de 2008

Por la presente ceden y transfieren todos sus derechos, título e interés sobre el mismo a **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, residente en Binger Str. 173, 55216

Eduardo Calado N.
Eduardo Calado Noguera
TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

Ingelheim am Rhein, Alemania, entidad a la cual se han cedido todos los derechos y el título sobre dicho invento en los siguientes territorios, a saber:

ARGENTINA, BRAZIL, CANADA, CHILE, CHINA, COLOMBIA, ECUADOR, EGIPTO, INDIA, INDONESIA, PAKISTAN, PERÚ, AFRICA DEL SUR, TAIWAN, TAILANDIA, URUGUAY, VENEZUELA, VIET NAM, LOS ESTADOS MIEMBROS DEL CONSEJO DE COOPERACION DEL GOLFO PERSICO Y LOS EMIRATOS ÁRABES UNIDOS, sin ninguna restricción.

Firmado: RICCARDO GIOVANNINI,

Se certifica la conformidad de la copia anterior con el original. Ingelheim am Rhein, 13 de julio de 2010/Ke

Firmado: notario público

APOSTILLE 1280/2010.

Nota del traductor: A continuación aparece otra cesión del mismo tenor que la anterior, pero firmada por los inventores siguientes: Cornelia DORNER-CIOSSEK, el 17 de marzo de 2009; Christian EICKMEIER, 17 de marzo de 2009; Dennis Fiegen, 1 de abril de 2009; Thomas FOX, 23 de marzo de 2009; Niklas HEINE, 23 de marzo de 2009; Holger ROSENBROCK, 17 de marzo de 2009 y Gerhard SCHAENZLE, 23 de marzo de 2009.

Se certifica la conformidad de la copia anterior con su respectivo original. Ingelheim am Rhein, 13 de julio de 2010.

Firma ilegible: notario público.

APOSTILLE 1279/2010

COLO-9255-841-151-5

ECN\ECN\ID-170545\WPCL002G

2 horas, 416 palabras

Bogotá, 10 de septiembre de 2010.

Eduardo Calado N.

Eduardo Calado Noguera
TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

La presente traducción oficial **No. 0102A/10** *fue elaborada por Hernando Torres Barrera, Traductor e Intérprete Oficial, según Resolución 01305 de 1998 del Ministerio de Justicia y del Derecho.*

---

*A continuación se traduce una apostilla en alemán, que acompaña a una certificación notarial en idioma inglés, en un DOCUMENTO DE CESIÓN (**Assignment of Inventors**).*

Präsidentin des Landgerichts 3 Mainz

APOSTILLA

(Convention de la Haye du 5 octobre 1961)

1. País: República Federal de Alemania

Este documento público

2. está firmado por Horst Heintskill
3. en su calidad de Notario
4. lleva el sello/timbre de Horst Heintskill - Notario en Ingelheim am Rhein

Certificado

5. en Maguncia
6. el 15 de julio de 2010
7. por la Presidenta del Tribunal Regional
8. bajo el No. 1280/2010
9. Sello/timbre
10. Firma

Marliese Dicke

Factura de gastos:
Tasa por impartir la legalización
Valor: 3.000,00 €
JVKostO[1] del. 26.7.1957
en conexión con § 45 KostO[2]
Tasa: 10,00 €

Maguncia, 15.07.10

Beyer

Funcionaria de justicia

SELLO: PRESIDENTA DEL TRIBUNAL REGIONAL * MAGUNCIA *

Bogotá, D.C., 6 de septiembre de 2010

[1] JVKostO = Reglamento de gastos de administración de justicia.
[2] KostO = Reglamento de gastos notariales

HERNANDO TORRES BARRERA
TRADUCTOR-E INTERPRETE OFICIAL
RES. No. 1305 MINJUSTICIA 1998

MINISTERIO DE
RELACIONES EXTERIORES

2010 SET 1 [illegible] 1:23

JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO

032044

Hernando Torres

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
AS FUNCIONES INDICADAS

La presente traducción oficial **No. 0102B/10** *fue elaborada por Hernando Torres Barrera, Traductor e Intérprete Oficial, según Resolución 01305 de 1998 del Ministerio de Justicia y del Derecho.*

26

---

*A continuación se traducen una certificación notarial y una apostilla en alemán, que acompañan un DOCUMENTO DE CESIÓN (**Assignment of Inventors**).*

Protocolo Notarial 1 UR 192 / 2009 — 1 UZ 199 / 2009

Notaría 1 Biberach a.d. Riß* Tel.: 07351/180310*Fax 07351/180366

Certificación Notarial

Por el presente certifico públicamente la autenticidad de las firmas que anteceden, de:

1. la señora Dra. Cornelia Dorner-Ciossek, apellido de soltera Dorner,
   fecha de nacimiento 20.09.1970,
   residente en 88447 Warthausen, Hanns-Wanner-Weg 9,

   - identificada con documento de identificación personal -

2. el señor Dr. Christian Eickmeier,
   fecha de nacimiento 08.07.1966,
   residente en 88441 Mittelbiberach, Ayestrasse 10/2,

   - identificado con documento de identificación personal -

3. el señor Dr. Dennis Fiegen,
   fecha de nacimiento 11.01.1977,
   residente en 88400 Biberach, Zwingergasse 9,

   - a quien conozco personalmente –

4. el señor Dr. Thomas Fox,
   fecha de nacimiento 21.07.1964,
   residente en 88400 Biberach, Grüner Weg 11,

   - identificado con pasaporte –

5. el señor Dr. Klaus Fuchs,
   fecha de nacimiento 28.03.1963,
   residente en 88441 Mittelbiberach, Klingenaecker 27,

   - identificado con documento de identificación personal –

6. el señor Dr. Niklas Heine,
   fecha de nacimiento 04.08.1971,
   residente en 88400 Biberach, Georg-Schinbain-Str. 66,

   - identificado con documento de identificación personal -

7. el señor Dr. Holger Rosenbrock,
   fecha de nacimiento 15.08.1969,
   residente en 88441 Mittelbiberach, Klingenäcker 14,

   - identificado con documento de identificación personal –

HERNANDO TORRES BARRERA
TRADUCTOR E INTERPRETE OFICIAL
RES. No. 1305 MINJUSTICIA 1998

8. el señor Dr. Gerhard Schänzle,
fecha de nacimiento 11.08.1967,
residente en 88400 Biberach, Sophie-von-La-Roche-Weg 10,

- a quien conozco personalmente -

puestas en mi presencia.

NOTARIAT
BIBERACH AN DER RISS

Biberach a.d. Riß, 01.04.2009

Notario

(Groß)

SELLO: NOTARÍA * BIBERACH AN DER RISS *

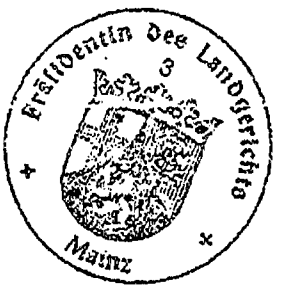
§§ KostO[1]	Concepto	Valor transacción	Importe
§§ 45 I, 141, 32 KostO	Autenticación de firmas	50.000,00 €	33,00 €
§§ 58 I, 141, 32 KostO	Tasa externa	50.000,00 €	30,00 €
§§ 58 I, 141, 32 KostO	Tasa externa	50.000,00 €	30,00 €
§§ 58 I, 141, 32 KostO	Tasa externa	50.000,00 €	30,00 €
	IVA 19,00% sobre	123,00 €	23,37 €
Total:			**146,37 €**

Factura No. 103661

[1] Reglamento de gastos notariales

HERNANDO TORRES BARRERA
TRADUCTOR E INTERPRETE OFICIAL
RES. No. 1305 MINJUSTICIA 1998

28



APOSTILLA

(Convention de la Haye du 5 octobre 1961)

1. País: República Federal de Alemania

Este documento público

2. está firmado por Horst Heintskill
3. en su calidad de Notario
4. lleva el sello/timbre de Horst Heintskill - Notario en Ingelheim am Rhein

Certificado

5. en Maguncia **6.** el 15 de julio de 2010
7. por la Presidenta del Tribunal Regional
8. bajo el No. 1279/2010
9. Sello/timbre **10.** Firma

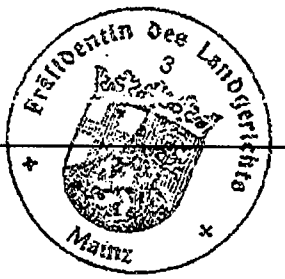
Marliese Dicke

Cuenta de gastos:
Tasa por impartir la legalización
Valor: 3.000,00 €
JVKostO[1] del. 26.07.1957
en conexión con § 45 KostO[2]
Tasa: 10,00 €

Maguncia, 15.07.2010

Beyer

Funcionaria de la administración de justicia



SELLO: PRESIDENTA DEL TRIBUNAL REGIONAL * MAGUNCIA *

Bogotá, D.C., 6 de septiembre de 2010

[1] JVKostO = Reglamento de gastos de administración de justicia.
[2] KostO = Reglamento de gastos notariales

HERNANDO TORRES BARRERA
TRADUCTOR E INTERPRETE OFICIAL
RES. No. 1305 MINJUSTICIA 1998

MINISTERIO DE
RELACIONES EXTERIORES

2010 SET 13 P 1:23

JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO

032045

Hernando Torres

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, 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.

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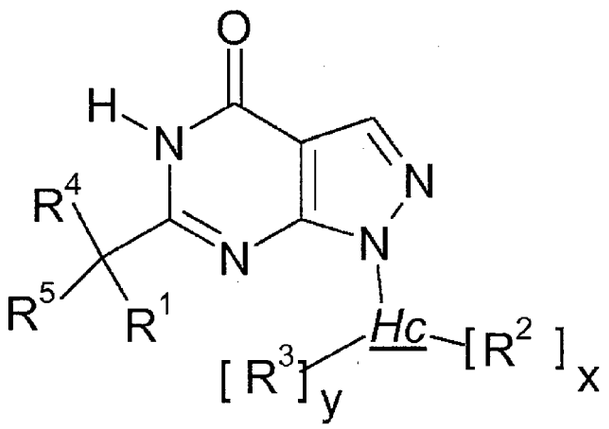
[Continued on next page]

(54) Title: 1-HETEROCYCLYL-1,5-DIHYDRO-PYRAZOLO[3,4-D] PYRIMIDIN-4-ONE DERIVATIVES AND THEIR USE AS PDE9A MODULATORS



(I)

(57) Abstract: The invention relates to novel 1,6-disubstituted pyrazolopyrimidinones, Formula (I) with is a mono-, bi- or tricyclic heterocyclyl group, the ring members of which are carbon atoms and at least 1, preferably 1, 2 or 3, heteroatom(s), which are selected from the group of nitrogen, oxygen and sulphur, which is in the form of -S(O)$_r$ - with r being 0, 1 or 2, and - said heterocyclyl group is or comprises 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member and - said heterocyclyl group is bound to the scaffold by said 1 non- aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member. According to one aspect of the invention the new compounds are for the manufacture of medicaments, in particular medicaments for the treatment of conditions concerning deficits in perception, concentration, learning or memory. The new compounds are also for the manufacture of medicaments for the treatment of Alzheimer's disease.

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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:

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1-HETEROCYCLYL-1,5-DIHYDRO-PYRAZOLO[3,4-D]PYRIMIDIN-4-ONE DERIVATIVES AND THEIR USE AS PDE9A MODULATORS

The invention relates to novel 1,6-disubstituted pyrazolopyrimidinones, wherein i.) the nitrogen atom of the pyrazolo-group that is next to the pyrimidino-group is attached to a non-aromatic, organic heterocycle having at least one ring hetero atom selected from O, N and S and ii.) to the C-atom between the two nitrogen atoms of the pyrimidinone-ring a second substituent is bound via an optionally substituted methylene-bridge. According to one aspect of the invention the new compounds are for the manufacture of medicaments, in particular medicaments for the treatment of conditions concerning deficits in perception, concentration, learning or memory. The new compounds are also for the manufacture of medicaments for the treatment of Alzheimer's disease. Further aspects of the present invention refer to a process for the manufacture of the compounds and their use for producing medicaments.

BACKGROUND OF THE INVENTION

The inhibition of phosphodiesterase 9A (PDE9A) is one of the currents concepts to find new access paths to the treatment of cognitive impairments due to CNS disorders like Alzheimer's Disease or due to any other neurodegenerative process of the brain. With the present invention, new compounds are presented that follow this concept.

Phosphodiesterase 9A is one member of the wide family of phosphodiesterases. These kinds of enzymes modulate the levels of the cyclic nucleotides 5'-3' cyclic adenosine monophosphate (cAMP) and 5'-3' cyclic guanosine monophosphate (cGMP). These cyclic nucleotides (cAMP and cGMP) are important second messengers and therefore play a central role in cellular signal transduction cascades. Each of them reactivates inter alia, but not exclusively, protein kinases. The protein kinase activated by cAMP is called protein kinase A (PKA), and the protein kinase activated by cGMP is called protein kinase G (PKG). Activated PKA and PKG are able in turn to phosphorylate a number of cellular effector proteins (e.g. ion channels, G-protein-coupled receptors, structural proteins, transcription factors). It is possible in this way for the second messengers cAMP and cGMP to control a wide variety of physiological processes in a wide variety of organs. However, the cyclic nucleotides

are also able to act directly on effector molecules. Thus, it is known, for example, that cGMP is able to act directly on ion channels and thus is able to influence the cellular ion concentration (review in: Wei *et al.*, *Prog. Neurobiol.*, **1998**, *56*, 37-64). The phosphodiesterases (PDE) are a control mechanism for controlling the activity of cAMP and cGMP and thus in turn for the corresponding physiological processes. PDEs hydrolyse the cyclic monophosphates to the inactive monophosphates AMP and GMP. Currently, 11 PDE families have been defined on the basis of the sequence homology of the corresponding genes. Individual PDE genes within a family are differentiated by letters (e.g. PDE1A and PDE1B). If different splice variants within a gene also occur, this is then indicated by an additional numbering after the letters (e.g. PDE1A1).

Human PDE9A was cloned and sequenced in 1998. The amino acid identity with other PDEs does not exceed 34 % (PDE8A) and is never less than 28 % (PDE5A). With a Michaelis-Menten constant (Km) of 170 nanomolar, PDE9A has high affinity for cGMP. In addition, PDE9A is selective for cGMP (Km for cAMP=230 micromolar). PDE9A has no cGMP binding domain, suggesting that the enzyme activity is not regulated by cGMP. It was shown in a Western blot analysis that PDE9A is expressed in humans inter alia in testes, brain, small intestine, skeletal muscle, heart, lung, thymus and spleen. The highest expression was found in the brain, small intestine, kidney, prostate, colon, and spleen (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564; Wang *et al.*, *Gene*, **2003**, *314*, 15-27). The gene for human PDE9A is located on chromosome 21q22.3 and comprises 21 exons. 4 alternative splice variants of PDE9A have been identified (Guipponi *et al.*, *Hum. Genet.*, **1998**, *103*, 386-392). Classical PDE inhibitors do not inhibit human PDE9A. Thus, IBMX, dipyridamole, SKF94120, rolipram and vinpocetine show no inhibition on the isolated enzyme in concentrations of up to 100 micromolar. An IC_{50} of 35 micromolar has been demonstrated for zaprinast (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564).

Murine PDE9A was cloned and sequenced in 1998 by Soderling *et al.* (*J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). This has, like the human form, high affinity for cGMP with a Km of 70 nanomolar. Particularly high expression was found in the

mouse kidney, brain, lung and liver. Murine PDE9A is not inhibited by IBMX in concentrations below 200 micromolar either; the IC_{50} for zaprinast is 29 micromolar (Soderling *et al.*, *J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). It has been found that PDE9A is strongly expressed in some regions of the rat brain. These include olfactory bulb, hippocampus, cortex, basal ganglia and basal forebrain (Andreeva *et al.*, *J. Neurosci.*, **2001**, *21* (22), 9068-9076). The hippocampus, cortex and basal forebrain in particular play an important role in learning and memory processes. As already mentioned above, PDE9A is distinguished by having particularly high affinity for cGMP. PDE9A is therefore active even at low physiological concentrations, in contrast to PDE2A (Km=10 micromolar; Martins *et al.*, *J. Biol. Chem.*, **1982**, *257*, 1973-1979), PDE5A (Km=4 micromolar; Francis *et al.*, *J. Biol. Chem.*, **1980**, *255*, 620-626), PDE6A (Km=17 micromolar; Gillespie and Beavo, *J. Biol. Chem.*, **1988**, *263* (17), 8133-8141) and PDE11A (Km=0.52 micromolar; Fawcett *et al.*, *Proc. Nat. Acad. Sci.*, **2000**, *97* (7), 3702-3707). In contrast to PDE2A (Murashima *et al.*, *Biochemistry*, **1990**, *29*, 5285-5292), the catalytic activity of PDE9A is not increased by cGMP because it has no GAF domain (cGMP-binding domain via which the PDE activity is allosterically increased) (Beavo *et al.*, *Current Opinion in Cell Biology*, **2000**, *12*, 174-179). PDE9A inhibitors may therefore lead to an increase in the baseline cGMP concentration.

This outline will make it evident that PDE9A engages into specific physiological processes in a characteristic and unique manner, which distinguish the role of PDE9A characteristically from any of the other PDE family members.

WO04099210 discloses 6-arylmethyl-substituted pyrazolopyrimidinones which are PDE9 inhibitors. The compounds do not have a non-aromatic heterocyclic moiety in the 1 position of the pyrazolopyrimidine.

WO04096811 discloses heterocyclic bicycles as PDE9 inhibitors for the treatment of diabetes, including type 1 and type 2 diabetes, hyperglycemia, dyslipidemia, impaired glucose tolerance, metabolic syndrome, and/or cardiovascular disease.
Other prior art is directed to chemically similar nucleoside derivatives. As examples it is referred to WO02057425, which discloses nucleosides derivatives, which are inhibitors of RNA-dependent RNA viral polymerase, or WO01060315, which discloses nucleoside derivatives for the treatment of hepatitis C infection or

EP679657, which discloses compounds that serve as ribonucleoside analogues or US2002058635, which discloses purine L-nucleoside compounds, in which both the purine rings and the sugar are either modified, functionalized, or both. So the sugar for example must show at least one esterified OH group.

WO06084281 discloses inhibitors of the E1 acitvation enzyme that have a sulfonamid moiety.

WO05051944 discloses oxetane-containing nucleosides, for the treatment of nucleoside analogue related disorders such as disorders involving cellular proliferation and infection.

WO9840384 discloses pyrazolopyrimidinones which are PDE1, 2 and 5 inhibitors and can be employed for the treatment of cardiovascular and cerebrovascular disorders and disorders of the urogenital system.

CH396 924, CH396 925, CH396 926, CH396 927, DE1147234, DE1149013, GB937726 describe pyrazolopyrimidinones which have a coronary-dilating effect and which can be employed for the treatment of disturbances of myocardial blood flow.

US3732225 describes pyrazolopyrimidinones which have an anti-inflammatory and blood glucose-lowering effect.

DE2408906 describes styrylpyrazolopyrimidinones which can be employed as antimicrobial and anti-inflammatory agents for the treatment of, for example, oedema.

OBJECTIVE OF THE INVENTION

The above cited prior art makes it evident that changes in the substitution pattern of pyrazolopyrimidinones result in interesting changes concerning biological activity, respectively changes in the affinity towards different target enzymes.

Therefore it is an objective of the present invention to provide compounds that effectively modulate PDE9A for the purpose of the development of a medicament, in particular in view of diseases, the treatment of which is accessible via PDE9A modulation.

It is another objective of the present invention to provide compounds that are useful for the manufacture of a medicament for the treatment of CNS disorders.

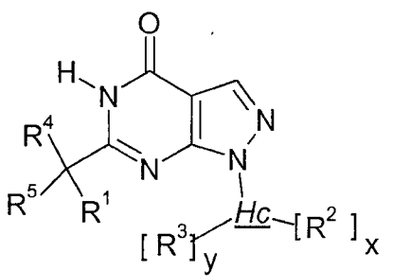
Yet another objective of the present invention is to provide compounds which show a better side effect profile compared to the compounds of the prior art.

Another objective of the present invention is to provide compounds that have a favourable selectively profile in favour for PDE9A inhibition over other PDE family members and by this may provide advantage over the prior art compounds.

Yet another objective is to provide such a medicament not only for treatment but also for prevention or modification of the corresponding disease.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The compounds of the present invention are characterised by general formula I:



(I),

with the following definitions (substituents may be printed in bold for better reading):

Substituent ***Hc*** is defined by the following definitions $\underline{\mathbf{Hc}}^{i}$, whereby the index i describes the order of preference, ascending from $\underline{\mathbf{Hc}}^{1}$ to more preferably (i.e. $\underline{\mathbf{Hc}}^{2}$), and so on:

$\underline{\mathbf{Hc}}^{1}$:

Hc is a mono-, bi- or tricyclic heterocyclyl group, the ring members of which are carbon atoms and at least 1, preferably 1, 2 or 3, heteroatom(s), which are selected

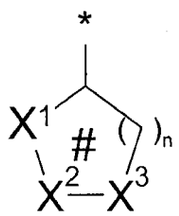
from the group of nitrogen, oxygen and sulphur, which is in the form of $-S(O)_r-$ with r being 0, 1 or 2, and

- said heterocyclyl group is or comprises 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member and
- said heterocyclyl group is bound to the scaffold by said 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member.

Hc²:

Hc is a heterocyclyl group according to any of formulae I.1 or I.2 or I.3:

formula I.1:



with

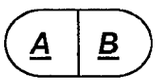
n = 1, 2, 3;

X^1, X^2, X^3, independently from each other being CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, or $S(O)_r$ with r = 0, 1, 2, whereby at least one of X^1, X^2, X^3 is O, NH, NR^2 or $S(O)_r$.

#: meaning that the ring is not aromatic while for n = 1, one bond within the ring system optionally may be a double bond and for n = 2 or n = 3 one bond or two bonds within the ring system optionally may be (a) double bond(s), thereby replacing ring-member bound hydrogen atoms. For each occasion the double bond preferably is a C-C double bond. Preferably the ring system is saturated.

The * represents the point of attachment to the nitrogen atom of the pyrazolo ring of formula I.

formula I.2:



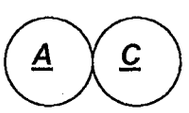
with

A being the ring system of formula I.1;

B being a 3, 4, 5 or 6 membered second ring system that is annelated to ***A*** and that besides the two atoms and one bond it shares with ***A*** consists only of carbon atoms and that may be saturated, partially saturated or aromatic; the substituents R^2 and/or R^3 independently of each other and independently of each x, y, may be at ring ***A*** or ring ***B***;

The two ring atoms that are shared by the two ring systems ***A*** and ***B*** both may be C-atoms, both may be N-atoms or one may be a C- and the other one may be a N-atom. Preferred are two C-atoms, or one C- and one N-atom, and more preferred are two C-atoms. The shared bond may be a single bond or a double bond.

formula I.3:



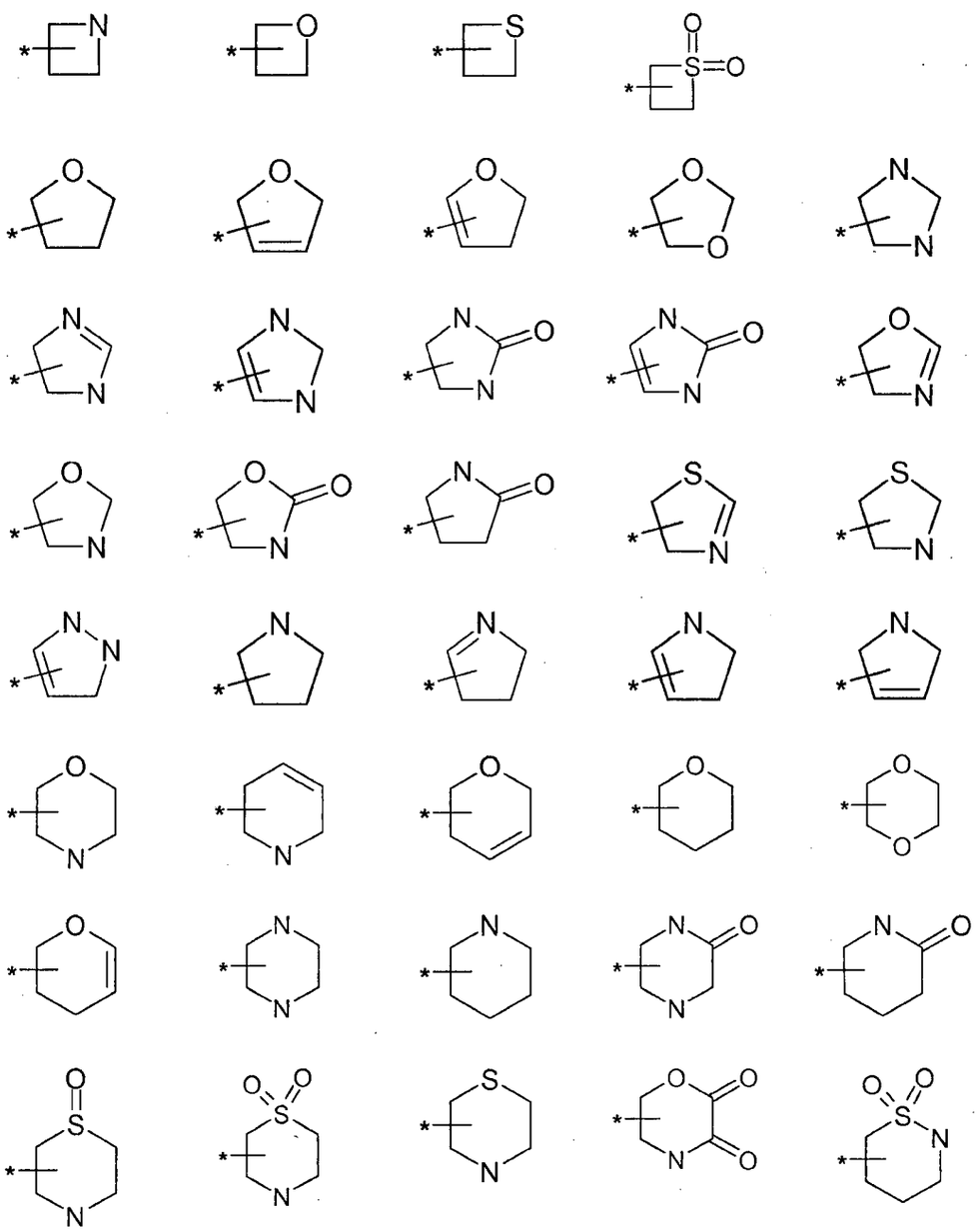
with

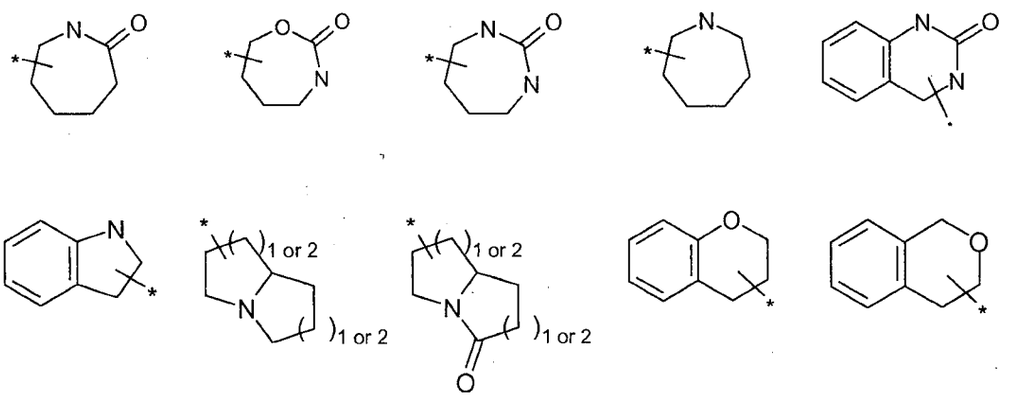
A, being the ring system of formula I.1;

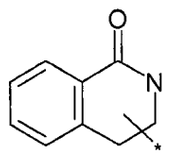
C being a 3, 4, 5 or 6 membered second ring system that is spiro fused to ***A*** and that besides the one atom it shares with ***A*** consists only of carbon atoms and that may be saturated or partially saturated; the substituents R^2 and/or R^3 independently of each other and independently of each x and y, may be at ring ***A*** or ring ***C***.

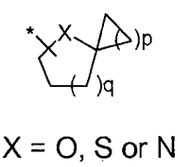
Hc^3:

Hc being a heterocyclyl group selected from the group of

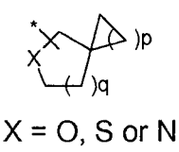




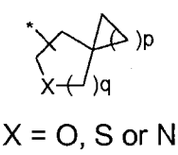




X = O, S or N
p = 1, 2, 3, 4 or 5
q = 1, 2 or 3



X = O, S or N
p = 1, 2, 3, 4 or 5
q = 1, 2 or 3



X = O, S or N
p = 1, 2, 3, 4 or 5
q = 1, 2 or 3

Hc^4:

Hc being the heterocyclyl group according to formula I.1 as defined above for **Hc^2**.

Hc^5:

Hc being the heterocyclyl group according to formula I.2 as defined above for **Hc^2**.

Hc^6:

Hc being the heterocyclyl group according to formula I.3 as defined above for **Hc^2**.

Hc$^{7.0}$:

Hc is a monocyclic, non-aromatic, saturated heterocyclic group of 4 to 8, preferably 5, 6 or 7 ring atoms, whereby said ring atoms are carbon atoms and 1, 2 or 3 heteroatom(s), preferably 1 heteroatom, the heteroatom(s) being selected from oxygen, nitrogen and sulphur, the sulphur being in the form of $-S(O)_r-$ with r being 0, 1 or 2, preferably with r being 0 and whereby preferably said heterocyclic group being attached to the scaffold by a carbon ring atom which is not directly attached to said ring heteroatom.

$Hc^{7.1}$:

Hc is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl and piperazinyl, whereby preferably the tetrahydropyranyl is 3- or 4-tetrahydropyranyl, the tetrahydrofuranyl is 3-tetrahydrofuranyl, and the piperidinyl is 3- or 4-piperidinyl.

Hc^{8}:

Hc is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl and pyrrolidinyl, whereby preferably the tetrahydropyranyl is 3- or 4-tetrahydropyranyl, the tetrahydrofuranyl is 3-tetrahydrofuranyl, and the piperidinyl is 3- or 4-piperidinyl.

Hc^{9}:

Hc is selected from the group of piperidinyl and pyrrolidinyl, preferably 3- or 4-piperidinyl and 3- pyrrolidinyl.

Hc^{10}:

Hc is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

Substituent R^1 is defined by the following definitions $R^{1.0.j}$, respectively $R^{1.j}$, whereby the index j describes the order of preference, ascending from $R^{1.0.1}$ to more preferred definitions like $R^{1.0.2}$, and so on to $R^{1.1}$, to $R^{1.2}$ and so on:

$R^{1.0.1}$:

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{2-8}-alkenyl-, C_{2-8}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, aryl-C_{2-6}-alkenyl-, aryl-C_{2-6}-alkynyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, heteroaryl-C_{2-6}-alkenyl-, and heteroaryl-C_{2-6}-alkynyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-O-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, heteroaryl-O-, heteroaryl-C_{1-6}-alkyl-O-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, N-linked-pyridine-2-one-C_{1-6}-alkyl-O-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-O- with C_{3-7}-heterocycloalkyl being bound to O via one of its ring C-atoms, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-O- with C_{3-7}-heterocycloalkyl being bound to the C_{1-6}-alkyl- via one of its ring-C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-$(R^{10})N$-, R^{10}O-CO-$(R^{10})N$-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-$(R^{10})N$-C_{1-6}-alkyl-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-$(R^{10})N$-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, and/or C_{1-6}-alkyl-SO_2-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl-, heteroaryl-, N-linked-pyridine-2-one-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-(R^{10})N-, $(R^{10})_2N$-SO_2-(R^{10})N-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, and/or C_{1-6}-alkyl-SO_2-.

$R^{1.0.2}$:

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-

atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, benzyl-O-, and/or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-.

$R^{1.0.3}$:

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, CF_3O-, CF_3-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, HO-C_{1-6}-alkyl-, oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, $(R^{10})_2N$-CO- and/or phenyl,

whereby the oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, CH_3-, CF_3-, CH_3O-, CF_3O-, H_2NCO-, NC-, morpholinyl and/or benzyl-O-.

$R^{1.0.4}$:

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, CH_3-, CH_3O-, H_2NCO- and/or NC-.

$R^{1.1}$:

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{2-8}-alkenyl-, C_{2-8}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{3-}

$_{7}$-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-O-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, heteroaryl-O-, heteroaryl-C_{1-6}-alkyl-O-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-O- with C_{3-7}-heterocycloalkyl being bound to O via one of its ring C-atoms, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-O- with C_{3-7}-heterocycloalkyl being bound to the C_{1-6}-alkyl- via one of its ring-C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, and C_{1-6}-alkyl-SO_2-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl-, heteroaryl-groups mentioned above may optionally be substituted by HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-(R^{10})N-, $(R^{10})_2N$-SO_2-(R^{10})N-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, or C_{1-6}-alkyl-SO_2-.

$R^{1.2}$:

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, aryl and heteroaryl,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}O-CO-O-, and R^{10}O-CO-(R^{10})N-;

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-groups mentioned above may optionally be substituted by NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-.

$R^{1.3}$:

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents selected from the group consisting of HO-, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, CF_3O-, CF_3-, fluorine, chlorine, bromine, C_{3-7}-heterocycloalkyl- and C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-.

$R^{1.4}$:

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents selected from the group consisting of NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3- and halogen (the halogen preferably being selected from the group of fluorine, chlorine, and bromine).

Optional substituent R^2 is defined by the following definitions $R^{2.0.k}$, respectively $R^{2.k}$, whereby the index k describes the order of preference, ascending from $R^{2.0.1}$ to more preferred definitions (like $R^{2.2}$), and so on:

$R^{2.0.1}$:

R^2 independently of any other R^2 being selected from the group of

H-, fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxy-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, preferably C_{1-6}-alkyl-S-C_{2-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, aryl-C_{2-6}-alkenyl-, aryl-C_{2-6}-alkynyl-, heteroaryl-, heteroaryl-C_{1-6}-alkyl-, heteroaryl -C_{2-6}-alkenyl-, heteroaryl -C_{2-6}-alkynyl-, R^{10}-O-C_{2-3}-alkyl-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, R^{10}-O-CO-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-, C_{1-6}-alkyl-SO_2- and oxo,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of

fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-,

and in case $\mathbf{R^2}$ is attached to a nitrogen which is a ring member of ***Hc***, this $\mathbf{R^2}$ shall be independently of any other R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of

fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-.

$\mathbf{R^{2.1}}$:

$\mathbf{R^2}$ independently of any other $\mathbf{R^2}$ being selected from the group of

H-, fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxy-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{2-3}-alkyl-, $(R^{10})_2N$-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-(R^{10})N-, R^{10}-CO-, $(R^{10})_2N$-CO-(R^{10})N-, R^{10}-SO_2-(R^{10})N-, and C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-,

and in case $\mathbf{R^2}$ is attached to a nitrogen which is a ring member of ***Hc***, this $\mathbf{R^2}$ shall be independently of any other R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-.

$\mathbf{R^{2.2}}$:

$\mathbf{R^2}$ independently of any other $\mathbf{R^2}$ being selected from the group of

H-, fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), $(R^{10})_2N$-CO- and R^{10}-CO-$(R^{10})N$-,

where the above-mentioned members may optionally be substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, NC-,

O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-,

and in case **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-.

$R^{2.3}$:

R^2 independently of any other **R^2** being selected from the group of

H-, fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), $(R^{10})_2N$-CO- and R^{10}-CO-$(R^{10})N$-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine and C_{1-6}-alkyl-,

and in case **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, or C_{1-6}-alkyl-SO_2-,

where these substituents may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and C_{1-6}-alkyl-.

$R^{2.4}$:

R^2 independently of any other R^2 being selected from the group of

H- and C_{1-6}-alkyl- (preferably C_{2-6}-alkyl),

and in case R^2 is attached to a nitrogen which is a ring member of ***Hc***, then R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, phenyl-CO- and phenyl-O-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and C_{1-6}-alkyl-.

$R^{2.5}$:

R^2 independently of any other R^2 being selected from the group of H- and C_{1-6}-alkyl-,

and in case R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2 H-, C1-6-alkyl-CO-, C1-6-alkyl-O-CO-, C1-6-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C1\text{-}6\text{-}alkyl)_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents.

Optional substituent $\mathbf{R^3}$ is defined by the following definitions $\mathbf{R^{3.l}}$ whereby the index l describes the order of preference, ascending from (i.e. $\mathbf{R^{3.1}}$) to preferably (i.e. $\mathbf{R^{3.2}}$), and so on:

$\mathbf{R^{3.1}}$:

$\mathbf{R^3}$ being selected from the group of H-, hydroxy and R^{10}-O-.

$\mathbf{R^{3.2}}$:

$\mathbf{R^3}$ being selected from the group of H-, hydroxyl and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-.

$\mathbf{R^{3.3}}$:

$\mathbf{R^3}$ being H.

Substituents $\mathbf{R^4}$ and $\mathbf{R^5}$ are defined by the following definitions $\mathbf{R^{4/5.m}}$ whereby the index m describes the order of preference, ascending from (i.e. $\mathbf{R^{4/5.1}}$) to preferably (i.e. $\mathbf{R^{4/5.2}}$), and so on:

$\mathbf{R^{4/5.1}}$:

$\mathbf{R^4}$ and $\mathbf{R^5}$ independently of one another being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-,

or

R^4 and R^5 together with the carbon atom to which they are bound form a 3- to 6-membered cycloalkyl group,

where the above-mentioned members including the carbocyclic ring formed may optionally be substituted independently of one another by one or more substituents selected from the group consisting of
fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and (C_{1-6}-alkyl-)$_2$N-CO-.

$R^{4/5.2}$:

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine and methyl.

$R^{4/5.3}$:

R^4 and **R^5** being H-.

Substituent **R^{10}** is defined by the following definitions **$R^{10.0.n}$**, respectively **$R^{10.n}$**, whereby the index n describes the order of preference. The preference ascends from **$R^{10.0.1}$** to preferably **$R^{10.0.2}$**, and so on up to **$R^{10.4}$**:

$R^{10.0.1}$:

R^{10} independently from any other **R^{10}** being selected from the group of

H- (but not in case it is part of a group being selected from R^{10}O-CO-, R^{10}-SO_2- or R^{10}-CO-), F_3C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-3}-alkyl-, heteroaryl, and heteroaryl-C_{1-3}-alkyl-,

and in case where two **R**^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)- preferably, and in particular preferably in case of (R^{10})$_2$N-CO-, these two **R**^{10} together with said nitrogen atom they are bound to form a group selected from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,

and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl- and C_{1-6}-alkyl-O-.

R$^{10.0.2}$.

R^{10} independently from any other **R**^{10} being selected from the group of H- (but not in case it is part of a group being selected from R^{10}O-CO-, R^{10}-SO_2- or R^{10}-CO-), C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, aryl and heteroaryl,

and in case where two **R**^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)-

and preferably, and in particular preferably in case of (R^{10})$_2$N-CO-, these two **R**^{10} together with said nitrogen atom they are bound to form a group selected from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,

and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-.

$R^{10.0.3}$:

R^{10} independently from any other **R^{10}** being selected from the group of

H- (but not in case it is part of a group being selected from R^{10}O-CO-, R^{10}-SO_2- or R^{10}-CO-), C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, aryl and heteroaryl, preferably aryl is phenyl and also preferably heteroaryl is selected from the group of oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, and pyrimidinyl;

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-.

$R^{10.0.4}$:

R^{10} independently from any other **R^{10}** being selected from the group of C_{1-6}-alkyl-, phenyl and pyridyl and in case **R^{10}** is a substituent of a nitrogen atom **R^{10}** is selected from the group of H, C_{1-6}-alkyl-, phenyl and pyridyl;

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-.

$R^{10.0.5}$:

$\mathbf{R^{10}}$ independently from any other $\mathbf{R^{10}}$ being selected from the group of methyl-, ethyl- and tert.-butyl, and in case $\mathbf{R^{10}}$ is a substituent of a nitrogen atom $\mathbf{R^{10}}$ is selected from the group of H, methyl-, ethyl- and tert.-butyl;

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine(s).

$\mathbf{R^{10.1}}$:

$\mathbf{R^{10}}$ independently from any other $\mathbf{R^{10}}$ being selected from the group of H- (but not in case it is part of a group being selected from $R^{10}O$-CO-, R^{10}-SO_2- or R^{10}-CO-), F_3C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, aryl, aryl-C_{1-3}-alkyl-, heteroaryl, and heteroaryl-C_{1-3}-alkyl-,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)- preferably, and in particular preferably in case of $(R^{10})_2$N-CO-, these two R^{10} groups together with said nitrogen atom they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl, and

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl- and C_{1-6}-alkyl-O-.

$\mathbf{R^{10.2}}$:

$\mathbf{R^{10}}$ independently from any other $\mathbf{R^{10}}$ being selected from the group of

C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, aryl and heteroaryl,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the $-CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)- preferably, and in particular preferably in case of $(R^{10})_2N$-CO-, these two R^{10} together with said nitrogen they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,

and

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-.

$R^{10.3}$:

R^{10} independently from any other **R^{10}** being selected from the group of

C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, aryl and heteroaryl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-.

$R^{10.4}$:

R^{10} independently from any other **R^{10}** being selected from the group of C_{1-6}-alkyl-, phenyl and pyridyl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-.

x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, more preferably x = 0, 1 and more preferably x = 0; if not specified otherwise in the context;

y = 0, or 1, preferably y = 0, if not specified otherwise in the context;

with the proviso for each applicable embodiment of formula I of the invention - such as for example embodiments that comprise ***Hc***^{1} and ***Hc***^{3} - that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -CH_2- spacer.

The values of x and y are independent from each other.

The index symbols i, j, k, ł, m, n in $R^{1.j}$, $R^{2.k}$ etc. are indices, each of which shall have the meaning of an integer figure: 1, 2, 3, etc. so that each $R^{1.j}$, $R^{2.k}$ etc. represents a characterised, individual embodiment of the corresponding substituents for which $R^{1.j}$, $R^{2.k}$ etc. are the definitions.

So given the above definitions, a generic genius of compounds according to formula I is fully characterised by the term (Hc^i $R^{1.j}$ $R^{2.k}$ $R^{3.ł}$ $R^{4/5.m}$ $R^{10.n}$) if for each letter i, j, k, ł, m and n an individual figure is given whereby – if not indicated otherwise in a specific context - for each such embodiment (Hc^i $R^{1.j}$ $R^{2.k}$ $R^{3.ł}$ $R^{4/5.m}$ $R^{10.n}$) **x** shall be 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2 and **y** shall be 0 or 1 and with the proviso for each applicable embodiment of formula I of the invention that if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -CH_2- group.

In other words, each embodiment ($\underline{Hc}^{i}$ $R^{1.j}$ $R^{2.k}$ $R^{3.l}$ $R^{4/5.m}$ $R^{10.n}$) represents a fully characterised genius or subset genius according to the general formula I, i.e. a generic genius of compounds that is subject of the present invention.

Such embodiment defines the variables ***Hc***, R^1, R^2, R^3, R^4, R^5 and if applicable R^{10} of formula I and wherein – if not in a specific context indicated otherwise - **x** shall be 0, 1, 2, 3 or 4, preferably being 0, 1 or 2 and **y** shall be 0 or 1 and with the proviso for each applicable embodiment of formula I of the invention that if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ group.

In a **1st general aspect** of the present invention, the compound or compounds of the present invention is (are) defined by the following embodiment according to the general formula I characterised by

$\underline{Hc}^{1}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$

with

x independently from of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2

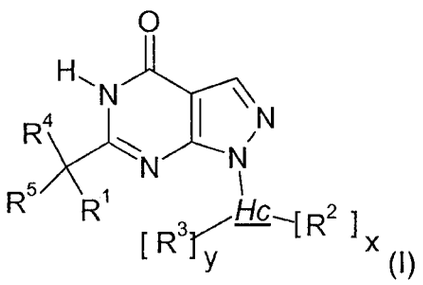
y independently of any x: **y** = 0 or 1,

and pharmaceutically acceptable salts and/or solvates and/or tautomeres etc. thereof;

with the proviso that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ spacer.

According to the above, this means that the 1st aspect of the present invention is related to compounds according to general formula I



(I)

with

Hc as defined by $\underline{\mathbf{Hc}}^{1}$;

$\mathbf{R}^{1}$ as defined by $\mathbf{R}^{1.0.1}$;

$\mathbf{R}^{2}$ as defined by $\mathbf{R}^{2.0.1}$;

$\mathbf{R}^{3}$ as defined by $\mathbf{R}^{3.1}$;

$\mathbf{R}^{4}$ and $\mathbf{R}^{4/}$as defined by $\mathbf{R}^{4/5.1}$;

$\mathbf{R}^{10}$ as defined by $\mathbf{R}^{10.0.1}$;

x independently from of any y: **x** being 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2;

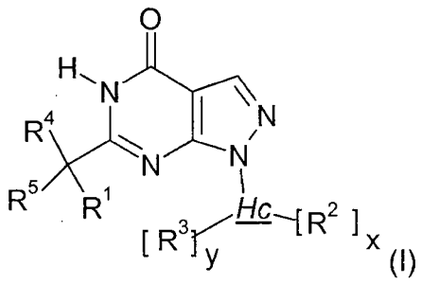
y independently of any x: **y** = 0 or 1;

and pharmaceutically acceptable salts and/or solvates and/or tautomeres etc. thereof;

with the proviso that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ spacer.

Thus this **1st aspect** of the inventions is defined as a compound according to general formula I



(I)

with

Hc is a mono-, bi- or tricyclic heterocyclyl group, the ring members of which are carbon atoms and at least 1, preferably 1, 2 or 3, heteroatom(s), which are selected from the group of nitrogen, oxygen and sulphur, which is in the form of $-S(O)_r-$ with r being 0, 1 or 2, and

- said heterocyclyl group is or comprises 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member and
- said heterocyclyl group is bound to the scaffold by said 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{2-8}-alkenyl-, C_{2-8}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, aryl-C_{2-6}-alkenyl-, aryl-C_{2-6}-alkynyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, heteroaryl-C_{2-6}-alkenyl-, and heteroaryl-C_{2-6}-alkynyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-O-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, heteroaryl-O-, heteroaryl-C_{1-6}-alkyl-O-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, N-linked-pyridine-2-one-C_{1-6}-alkyl-O-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-O- with C_{3-7}-heterocycloalkyl being bound to O via one of its ring C-atoms, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-O- with C_{3-7}-heterocycloalkyl being bound to the C_{1-6}-alkyl- via one of its ring-C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, and/or C_{1-6}-alkyl-SO_2-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl-, heteroaryl-, N-linked-pyridine-2-one-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-(R^{10})N-, $(R^{10})_2N$-SO_2-(R^{10})N-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, and/or C_{1-6}-alkyl-SO_2-;

R² independently of any other **R²** being selected from the group of:

H-, fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxy-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, preferably C_{1-6}-alkyl-S-C_{2-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, aryl-C_{2-6}-alkenyl-, aryl-C_{2-6}-alkynyl-, heteroaryl-, heteroaryl-C_{1-6}-alkyl-, heteroaryl -C_{2-6}-alkenyl-, heteroaryl -C_{2-6}-alkynyl-, R^{10}-O-C_{2-3}-alkyl-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, R^{10}-O-CO-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-, C_{1-6}-alkyl-SO_2- and oxo,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-,

and in case **R²** is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-;

R^3 being selected from the group of

H-, hydroxy and R^{10}-O-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-,

or

R^4 and R^5 together with the carbon atom to which they are bound form a 3- to 6-membered cycloalkyl group,

where the above-mentioned members including the carbocyclic ring formed may optionally be substituted independently of one another by one or more substituents selected from the group consisting of
fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and $(C_{1-6}$-alkyl-$)_2$N-CO-;

R^{10} independently from any other **R^{10}** being selected from the group of

H- (but not in case it is part of a group being selected from R^{10}O-CO-, R^{10}-SO_2- or R^{10}-CO-), F_3C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-3}-alkyl-, heteroaryl, and heteroaryl-C_{1-3}-alkyl-,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)-, preferably, and in particular preferably in case of $(R^{10})_2$N-CO-, these two R^{10} together with said nitrogen atom they are bound to form a group selected

from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl- and C_{1-6}-alkyl-O-;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof,

with the proviso for each applicable embodiment of formula I of the invention that

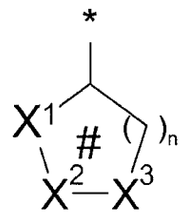
if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -CH_2-spacer*.

*This means that no substituent comprises a CH_2-group by which it is bound to oxetanyl.

A **2nd aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is a heterocyclyl group according to a formula being selected from the group of formulae I.1, I.2 and I.3:

formula I.1:



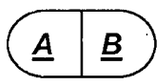
with

n = 1, 2, 3;

X^1, X^2, X^3, independently from each other being CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, or $S(O)_r$ with r = 0, 1, 2, whereby at least one of X^1, X^2, X^3 is O, NH, NR^2 or $S(O)_r$.;

#: meaning that the ring is not aromatic while for n = 1 one bond within the ring system optionally may be a double bond and for n = 2 or n = 3 one bond or two bonds within the ring system optionally may be (a) double bond(s), thereby replacing ring-member bound hydrogen atoms, whereby such double bond(s) preferably being a C-C double bond, more preferably the ring being saturated;

formula I.2:



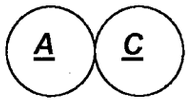
with

A being the ring system of formula I.1;

B being a 3, 4, 5 or 6 membered second ring system that is annelated to ***A*** and that besides the two atoms and one bond - which may be a single or a double bond - it shares with ***A*** consists only of carbon atoms and that may be saturated, partially saturated or aromatic; the substituents R^2 and/or R^3 independently of each other and

independently of each x or y may be at ring ***A*** or ring ***B***; whereby the two ring atoms that are shared by the two ring systems ***A*** and ***B*** both may be carbon atoms, both may be nitrogen atoms or one may be a carbon and the other one may be a nitrogen atom, whereby two carbon atoms or one carbon and one nitrogen atom are preferred and two carbon atoms are more preferred;

formula I.3:



with

A, being the ring system of formula I.1;

C being a 3, 4, 5 or 6 membered saturated or partially saturated second ring system that is spiro fused to ***A*** and that besides the one atom it shares with ***A*** consists only of carbon atoms and the substituents R^2 and/or R^3 independently of each other and independently of each x and y may be at ring ***A*** or ring ***C***;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-,

tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, benzyl-O-, and/or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other **R^2** being selected from the group of

H-, fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), $(R^{10})_2N$-CO- and R^{10}-CO-$(R^{10})N$-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine and C_{1-6}-alkyl-,

and in case **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and C_{1-6}-alkyl-;

R^3 being selected from the group of

H-, hydroxy, C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, and methyl;

R^{10} independently from any other **R^{10}** being selected from the group of

H- (but not in case it is part of a group being selected from R^{10}O-CO- or R^{10}-CO-), C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, aryl and heteroaryl,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)-, preferably, and in particular preferably in case of $(R^{10})_2$N-CO-, these two R^{10} together with said nitrogen atom they are bound to form a group selected from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

A **3rd aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is a monocyclic, non-aromatic, saturated heterocyclic group of 4 to 8, preferably 5, 6 or 7 ring atoms, whereby said ring atoms are carbon atoms and 1, 2 or 3 heteroatom(s), preferably 1 heteroatom, the heteroatom(s) being selected from oxygen, nitrogen and sulphur, the sulphur being in the form of $-S(O)_r-$ with r being 0, 1 or 2, preferably with r being 0 and whereby preferably said heterocyclic group being attached to the scaffold by a carbon ring atom which is not directly attached to said ring heteroatom;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-

C_{1-6}-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, benzyl-O-, and/or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other **R^2** being selected from the group of H- and C_{1-6}-alkyl-,

and in case **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other **R^2**: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}$-alkyl$)_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$\mathbf{R^4}$ and $\mathbf{R^5}$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably both being H;

$\mathbf{R^{10}}$ independently from any other $\mathbf{R^{10}}$ selected from the group of C_{1-6}-alkyl-, phenyl and pyridyl and in case $\mathbf{R^{10}}$ is a substituent of a nitrogen atom $\mathbf{R^{10}}$ is selected from the group of H, C_{1-6}-alkyl-, phenyl and pyridyl,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof,

with the proviso that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -CH_2-group*.

*This means that no substituent comprises a CH_2-group by which it is bound to oxetanyl.

A **4th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl and piperazinyl, whereby preferably the tetrahydropyranyl is 3- or 4-tetrahydropyranyl, the tetrahydrofuranyl is 3-tetrahydrofuranyl, and the piperidinyl is 3- or 4-piperidinyl; more preferably ***Hc*** is tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and thereof preferably , 3- and 4-tetrahydropyranyl, 3- and 4-piperidinyl and 3- pyrrolidinyl;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of

fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, benzyl-O-, and/or $(R^{10})_2$N-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other potential **R^2** being selected from the group of H- and C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}$-alkyl$)_2$N-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

R^{10} independently from any other **R^{10}** being selected from the group of C_{1-6}-alkyl-, phenyl and pyridyl and in case **R^{10}** is a substituent of a nitrogen atom **R^{10}** is selected from the group of H, C_{1-6}-alkyl-, phenyl and pyridyl,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

A **5th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl and piperazinyl, whereby preferably the tetrahydropyranyl is 3- or 4-tetrahydropyranyl, the tetrahydrofuranyl is 3-tetrahydrofuranyl, and the piperidinyl is 3- or 4-piperidinyl; more preferably ***Hc*** is tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and thereof preferably , 3- and 4-tetrahydropyranyl, 3- and 4-piperidinyl and 3- pyrrolidinyl;

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine,

bromine, iodine, oxo, HO-, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, CF_3O-, CF_3-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, HO-C_{1-6}-alkyl-, oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, $(R^{10})_2N$-CO- and/or phenyl,

whereby the oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, CH_3-, CF_3-, CH_3O-, CF_3O-, H_2NCO-, NC-, morpholinyl and/or benzyl-O-;

R^2 independently of any other potential **R^2** being selected from the group of H- and C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}$-alkyl$)_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxyl and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and R^5 independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

R^{10} independently from any other R^{10} is selected from the group of H, C_{1-6}-alkyl-, phenyl and pyridyl,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x independently from each other **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2. preferably **x** = 0 or 1, more preferably **x** = 0;

y independently from each other **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

A **6th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, piperazinyl, preferably tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and thereof preferably, 3- and 4-tetrahydropyranyl, 3- and 4-piperidinyl and 3- pyrrolidinyl;

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, CH_3-, CH_3O-, H_2NCO- and/or NC-;

R^2 independently of any other **R^2** being selected from the group of H- or C_{1-6}-alkyl-,

and in cases **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and R^5 independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

A **7th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is selected from the group of piperidinyl and pyrrolidinyl, preferably 3- or 4-piperidinyl and 3- pyrrolidinyl;

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents

independently of one another selected from the group consisting of fluorine, CH_3-, CH_3O-, H_2NCO- and/or NC-;

R^2 independently of any other **R^2** being selected from the group of H- and C_{1-6}-alkyl-,

and in cases **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}$-alkyl$)_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

A **8th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is selected from the group of piperidinyl and pyrrolidinyl, preferably 3- or 4-piperidinyl and 3- pyrrolidinyl;

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of each other selected from the group consisting of NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3- and halogen, the halogen preferably being selected from fluorine, chlorine and bromine.

R^2 independently of any other R^2 being selected from the group of H- and C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^4 and R^5 both being H

x = 0 or 1;

y = 0;

and pharmaceutically acceptable salts thereof.

An **9th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, CH_3-, CH_3O-, H_2NCO- and/or NC-;

R^2 independently of any other R^2 being selected from the group of H- and C_{1-6}-alkyl-,

where the above-mentioned C_{1-6}-alkyl-group(s) may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and R^5 independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, most preferably **x** = 0;

y independently of any x: **y** = 0, or 1, most preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

A **10th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of each other selected from the group consisting of NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3- and halogen, the halogen preferably being selected from fluorine, chlorine and bromine.

R^2 independently of any other **R^2** being selected from the group of H- and C_{1-6}-alkyl-,

where the above-mentioned C_{1-6}-alkyl-group(s) may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, most preferably **x** = 0;

y independently of any x: **y** = 0, or 1, most preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

An **11th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

Hc is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of each other selected from the group consisting of NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3- and halogen, the halogen preferably being selected from fluorine, chlorine and bromine.

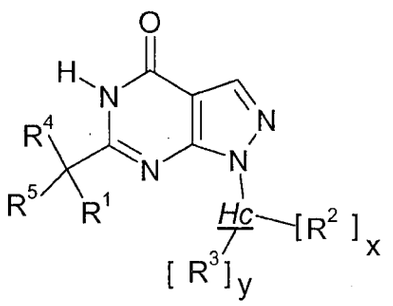
R^4 and R^5 both being H

x = 0;

y = 0;

and pharmaceutically acceptable salts thereof.

A **12th aspect** of the inventions concerns a compound according to general formula I



(I),

wherein;

Hc is a mono-, bi- or tricyclic heterocyclyl group, the ring members of which are carbon atoms and at least 1, preferably 1, 2 or 3, heteroatom(s), which are selected from the group of nitrogen, oxygen and sulphur, which is in the form of $-S(O)_r$ - with r being 0, 1 or 2, and

- said heterocyclyl group is or comprises 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member and
- said heterocyclyl group is bound to the scaffold by said 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member.

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{2-8}-alkenyl-, C_{2-8}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-,

HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-O-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, heteroaryl-O-, heteroaryl-C_{1-6}-alkyl-O-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-O- with C_{3-7}-heterocycloalkyl being bound to O via one of its ring C-atoms, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-O- with C_{3-7}-heterocycloalkyl being bound to the C_{1-6}-alkyl- via one of its ring-C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, and C_{1-6}-alkyl-SO_2-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl-, heteroaryl-groups mentioned above may optionally be substituted preferably independently of each other by HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-(R^{10})N-, $(R^{10})_2N$-SO_2-(R^{10})N-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, and C_{1-6}-alkyl-SO_2-;

R^2 independently of any other **R^2** being selected from the group of

H-, fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxy-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-

C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{2-3}-alkyl-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-, and C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-,

and in case **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-;

R^3 independently being selected from the group of H-, hydroxy and R^{10}-O-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-,

or

R^4 and R^5 together with the carbon atom to which they are bound form a 3- to 6-membered cycloalkyl group,

where the above-mentioned members including the carbocyclic ring formed may optionally be substituted independently of one another by one or more substituents selected from the group consisting of
fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and (C_{1-6}-alkyl-)$_2$N-CO-;

R^{10} independently from any other **R^{10}** being selected from the group of

H- (but not in case it is part of a group being selected from R^{10}O-CO-, R^{10}-SO_2- or R^{10}-CO-), F_3C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, aryl, aryl-C_{1-3}-alkyl-, heteroaryl, and heteroaryl-C_{1-3}-alkyl-,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)- preferably, and in particular preferably in case of (R^{10})$_2$N-CO-, these two R^{10} groups together with said nitrogen atom they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl- and C_{1-6}-alkyl-O-;

x independently from each other **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently from each other **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salt forms or solvates thereof,

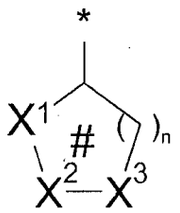
with the proviso that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -CH_2- spacer.

A **13th aspect** of the inventions concerns a compound according to general formula I of the 12th aspect of the invention, wherein

Hc is a heterocyclyl group according to a formula being selected from the group of formulae I.1, I.2 and I.3:

formula I.1:



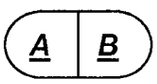
with

n = 1, 2, 3;

X^1, X^2, X^3, independently from each other being CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, or $S(O)_r$ with r = 0, 1, 2, whereby at least one of X^1, X^2, X^3 is O, NH, NR^2 or $S(O)_r$.;

#: meaning that the ring is not aromatic, while for n = 1 one bond within the ring system optionally may be a double bond and for n = 2 or n = 3 one bond or two bonds within the ring system optionally may be (a) double bond(s), thereby replacing ring-member bound hydrogen atoms, whereby such double bond(s) preferably being a C-C double bond, more preferably the ring being saturated;

formula I.2:

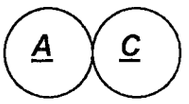


with

A being the ring system of formula I.1;

B being a 3, 4, 5 or 6 membered second ring system that is annelated to ***A*** and that besides the two atoms and one bond - which may be a single or a double bond - it shares with ***A*** consists only of carbon atoms and that may be saturated, partially saturated or aromatic; the substituents R^2 and/or R^3 independently of each other and independently of each x or y may be at ring ***A*** or ring ***B***; whereby the two ring atoms that are shared by the two ring systems ***A*** and ***B*** both may be carbon atoms, both may be nitrogen atoms or one may be a carbon and the other one may be a nitrogen atom, whereby two carbon atoms or one carbon and one nitrogen atom are preferred and two carbon atoms are more preferred;

formula I.3:



with

A, being the ring system of formula I.1;

C being a 3, 4, 5 or 6 membered saturated or partially saturated second ring system that is spiro fused to ***A*** and that besides the one atom it shares with ***A*** consists only of carbon atoms and the substituents R^2 and/or R^3 independently of each other and independently of each x and y may be at ring ***A*** or ring ***C***;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, aryl and heteroaryl,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, $R^{10}O$-CO-O-, and $R^{10}O$-CO-$(R^{10})N$-;

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-groups mentioned above may optionally be substituted preferably independently of each other by NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-

O-, R^{10}-CO-, R^{10}O-CO-, or $(R^{10})_2$N-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other **R^2** being selected from the group of

H-, fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), $(R^{10})_2$N-CO-, R^{10}-CO-(R^{10})N-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine and C_{1-6}-alkyl-,

and in case **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, R^{10}O-CO-, $(R^{10})_2$N-CO-, R^{10}-CO-, or C_{1-6}-alkyl-SO_2-,

where where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and C_{1-6}-alkyl-;

R^3 independently of any other **R^3** being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-; preferably **R^3** being H;

$\mathbf{R^4}$ and $\mathbf{R^5}$ independently of one another being selected from the group of H-, fluorine, and methyl; preferably independently of one another being H- or fluorine, more preferably $\mathbf{R^4}$ and $\mathbf{R^5}$ being H;

$\mathbf{R^{10}}$ independently from any other potential $\mathbf{R^{10}}$ being selected from the group of

C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, aryl and heteroaryl,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the $-CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)- preferably, and in particular preferably in case of $(R^{10})_2N$-CO-, these two R^{10} together with said nitrogen they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,

and

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

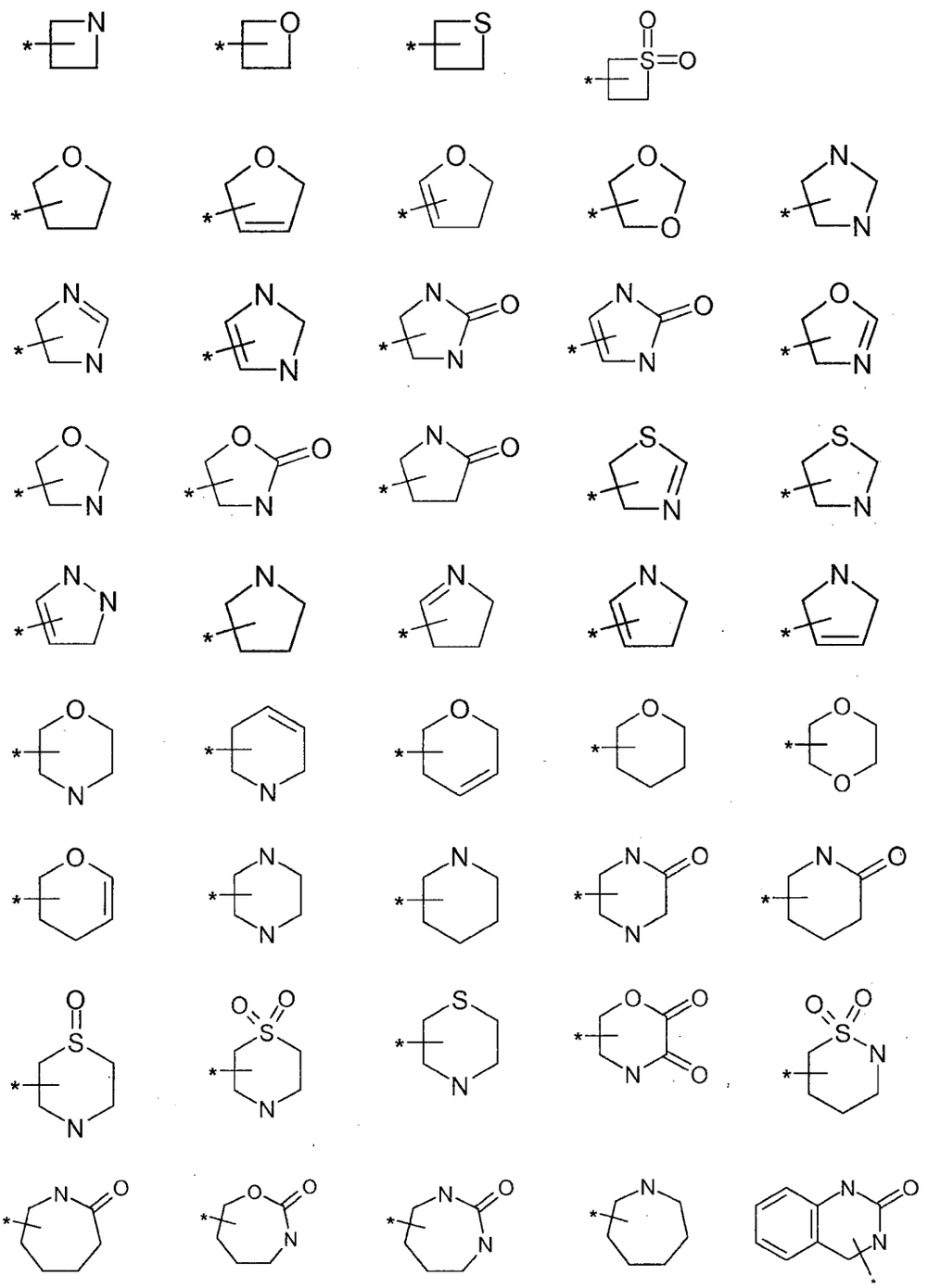
x independently from each other **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

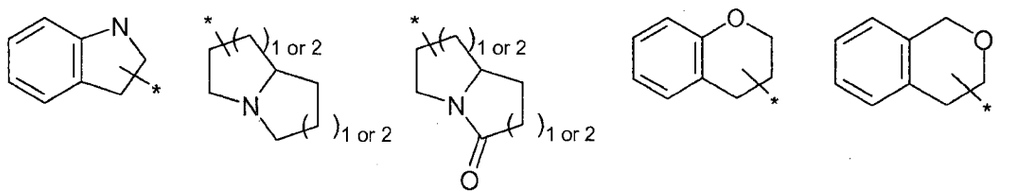
y independently from each other **y** = 0, or 1, more preferably **y** = 0;

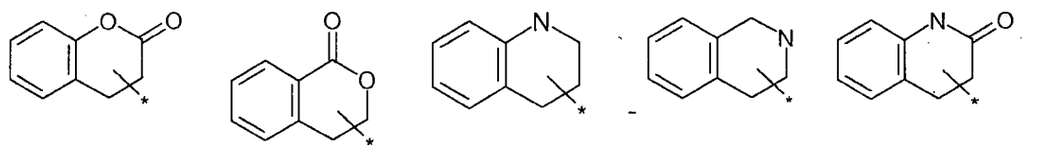
and pharmaceutically acceptable salt forms or solvates thereof.

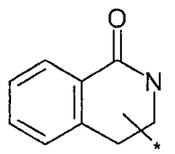
An **14th aspect** of the inventions concerns a compound according to general formula I of the 12th aspect of the invention, wherein

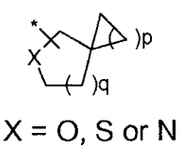
Hc being a heterocyclyl group selected from the group of

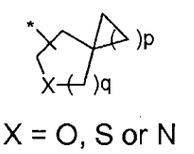












R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, aryl and heteroaryl,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}O-CO-O-, and R^{10}O-CO-(R^{10})N-;

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-groups mentioned above

may optionally be substituted preferably independently of each other by NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, or $(R^{10})_2$N-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other **R^2** being selected from the group of

H-, fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), $(R^{10})_2$N-CO-, R^{10}-CO-(R^{10})N-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine and C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, R^{10}O-CO-, $(R^{10})_2$N-CO-, R^{10}-CO-, or C_{1-6}-alkyl-SO_2-,

where where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and C1-6-alkyl-;

R^3 independently of any other **R^3** being selected from the group of

H-, hydroxyl and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and R^5 independently of one another being selected from the group of H-, fluorine, and methyl; preferably independently of one another being selected from the group of H- and fluorine, more preferably R^4 and R^5 being H;

R^{10} independently from any other R^{10} being selected from the group of

C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, aryl and heteroaryl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x independently from each other **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently from each other **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salt forms or solvates thereof

with the proviso that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -CH_2- spacer.

A **15th aspect** of the inventions concerns a compound according to the 13th aspect of the invention, wherein

Hc being selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl;

and

R^2 independently of any other **R^2** being H- or C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

and

R^4 and **R^5** being H

and

R^{10} independently from any other **R^{10}** being selected from the group of C_{1-6}-alkyl-, phenyl, and pyridyl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-.

A **16th aspect** of the inventions concerns a compound according to the 15th aspect of the invention, wherein

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents selected from the group consisting of HO-, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, CF_3O-, CF_3-, fluorine, chlorine, bromine, C_{3-7}-heterocycloalkyl- and C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-.

A **17th aspect** of the inventions concerns a compound with all features according to the 16th aspect of the invention, except in that

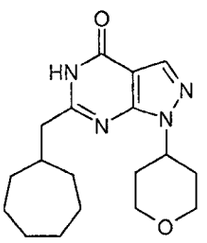
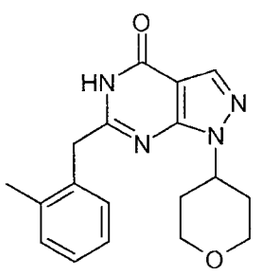
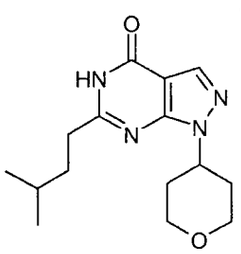
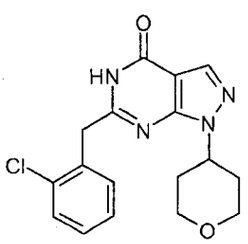
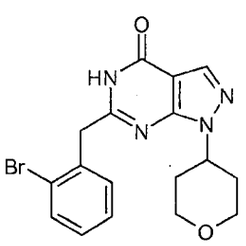
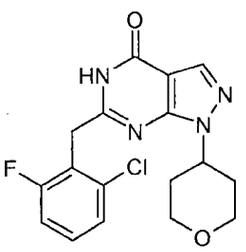
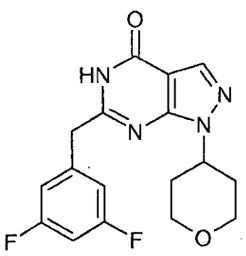
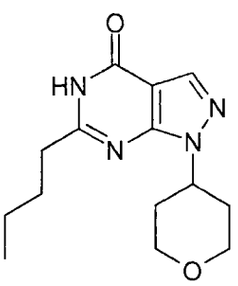
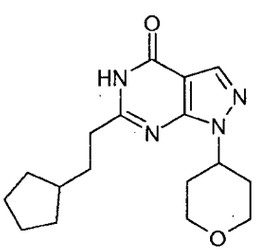
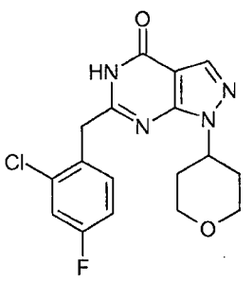
R^1 being selected from the group of

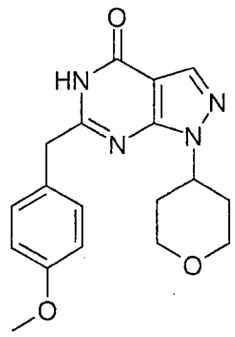
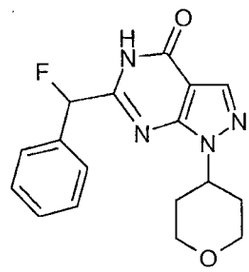
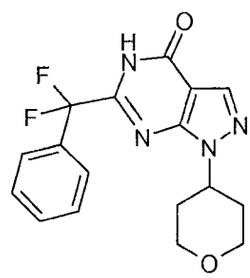
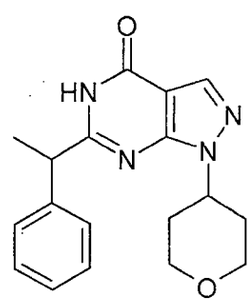
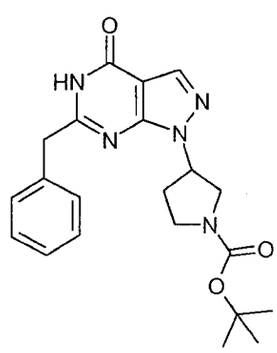
phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

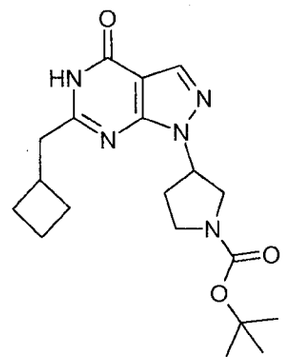
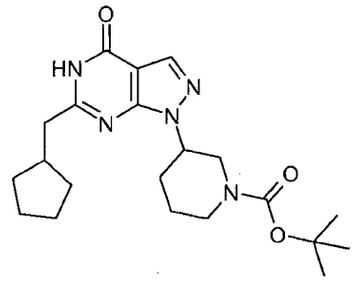
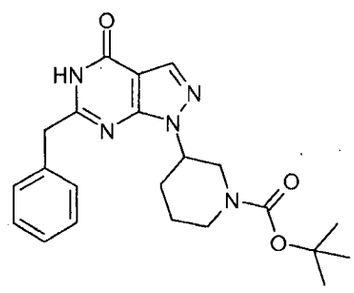
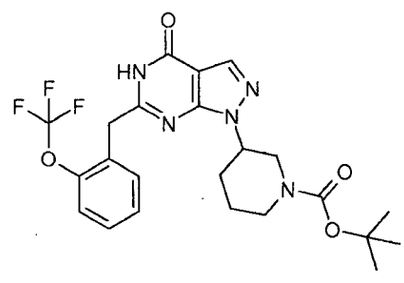
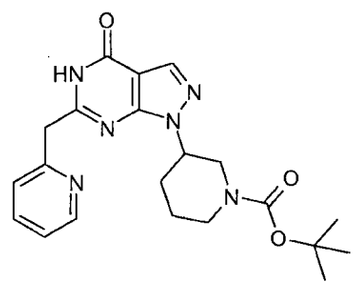
where these groups may optionally be substituted by one or more substituents selected from the group consisting of NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3- and halogen, the halogen preferably being selected from the group of fluorine, chlorine and bromine.

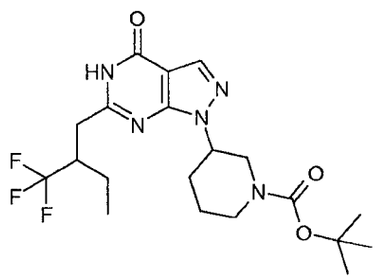
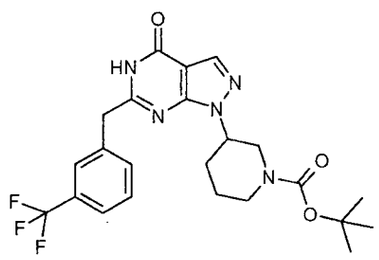
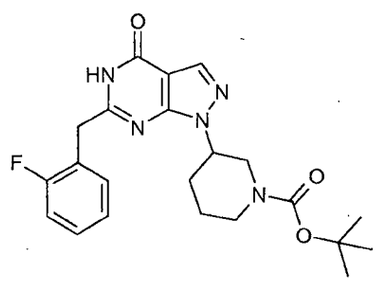
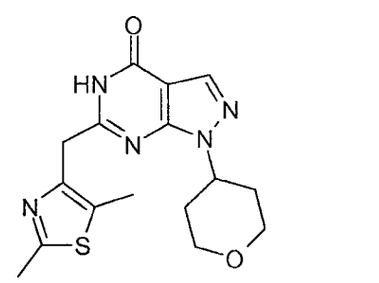
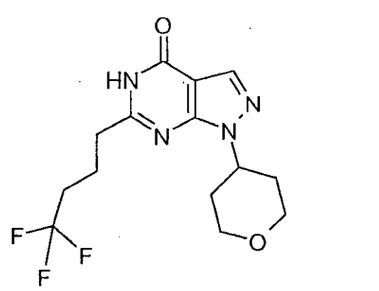
A **specific aspect** of the inventions **(18th aspect)** concerns - independently of each other and separable therefrom - each of the following compounds and/or wherever applicable each specific stereoisomer thereof and/or tautomer thereof and/or a pharmaceutically acceptable salt thereof. Each compound is represented and considered in form of the neutral compound without indicating the stereochemistry thereof if any. The left hand column indicates the example the compound derives from. Specific information concerning stereochemical properties can be taken from the experimental section, section **Exemplary embodiments**. In case the final compounds according to said section **Exemplary embodiments** are salts forms,

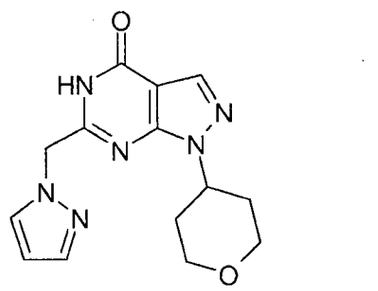
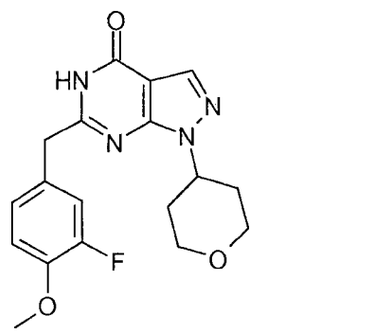
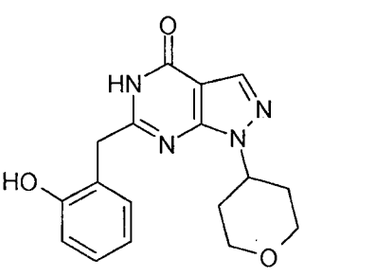
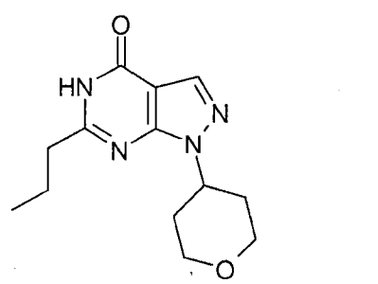
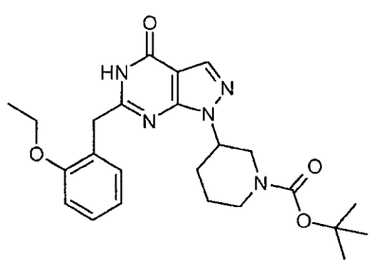
they can be converted into the neutral compound (free base or acid) by conventional methods.

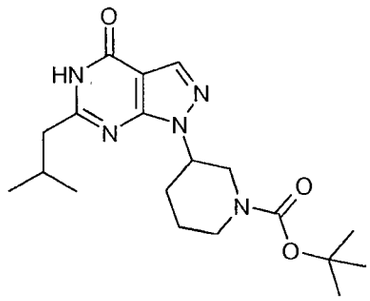
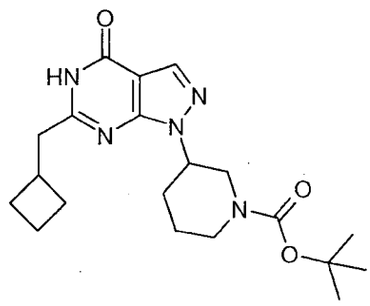
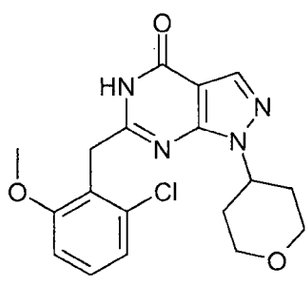
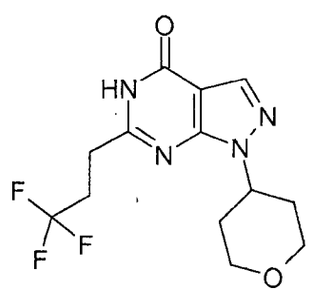
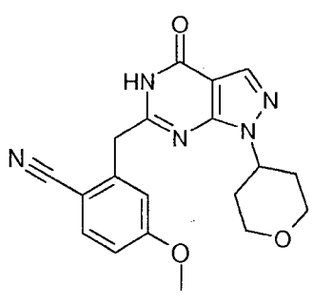
example No.	structure
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

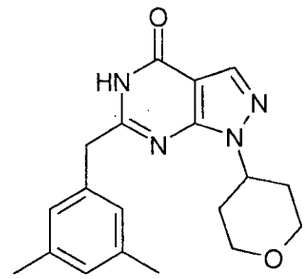
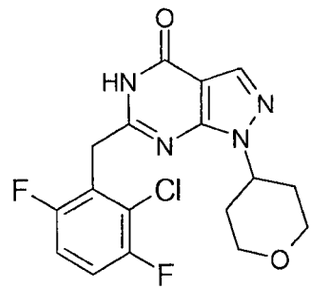
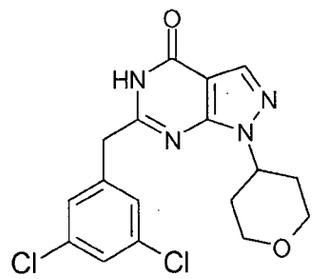
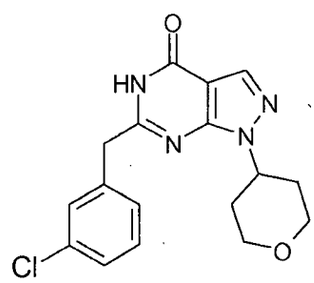
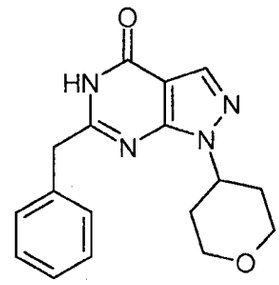
11	
12	
13	
14	
15	

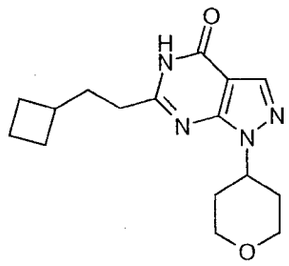
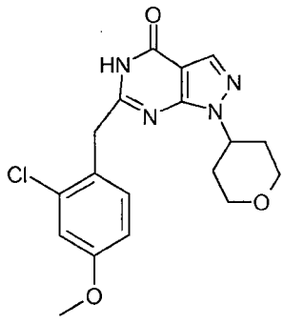
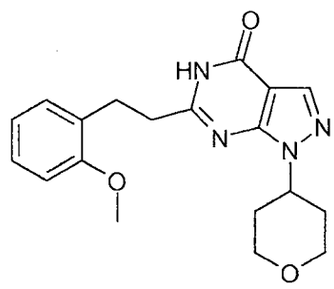
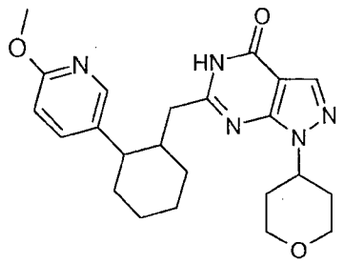
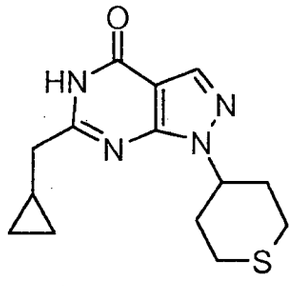
16	
17	
18	
19	
20	

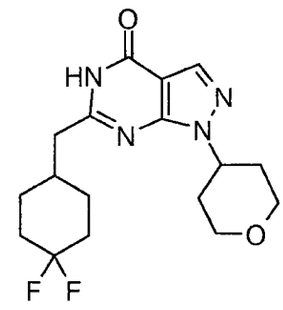
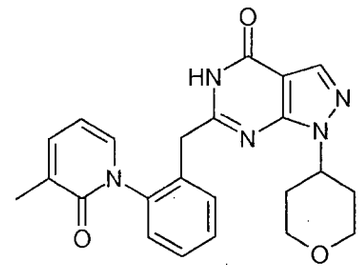
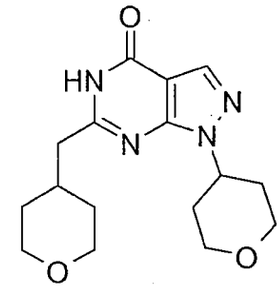
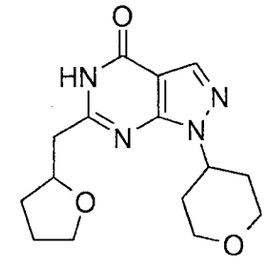
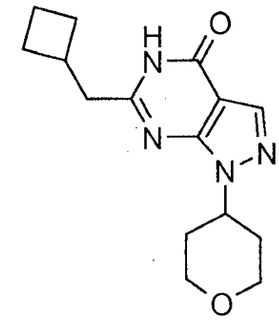
21	
22	
23	
24	
25	

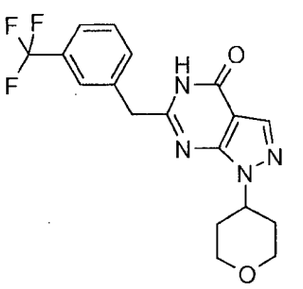
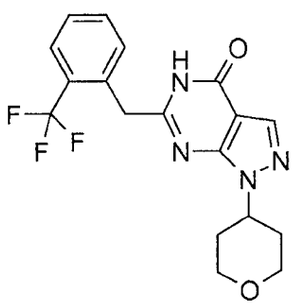
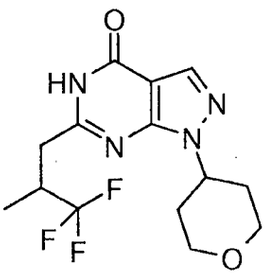
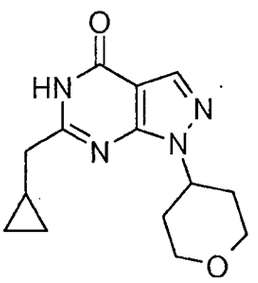
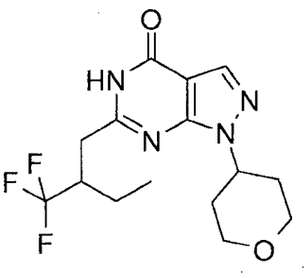
26	
27	
28	
29	
30	

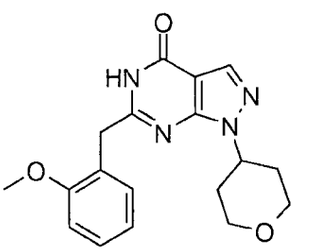
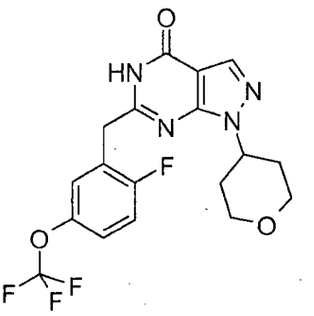
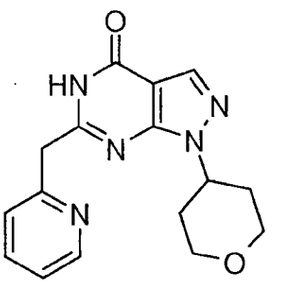
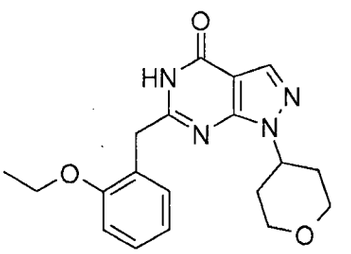
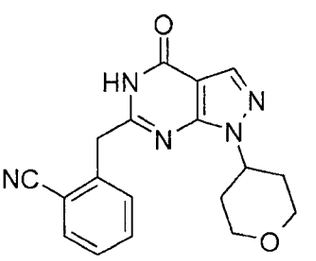
31	
32	
33	
34	
35	

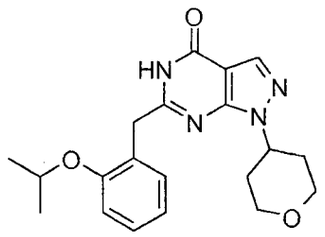
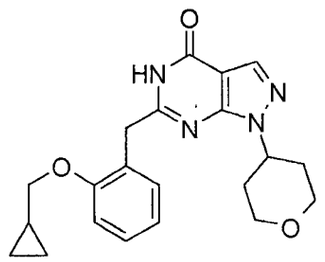
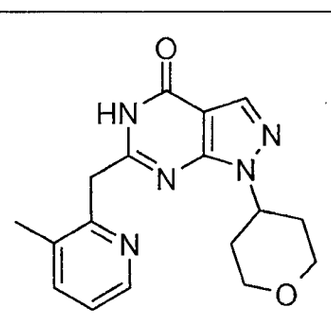
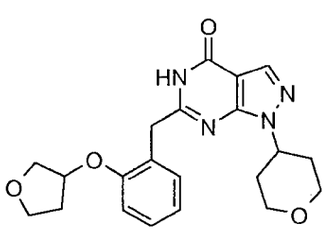
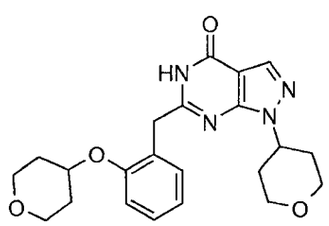
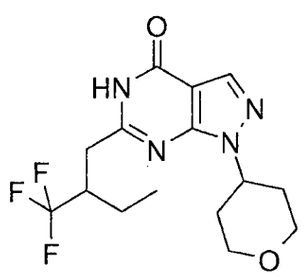
36	
37	
38	
39	
40	

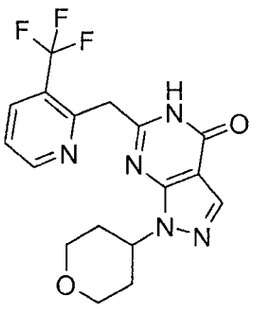
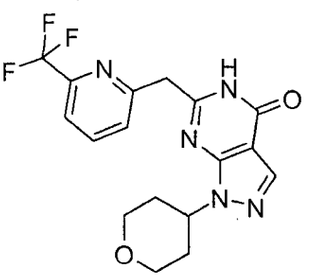
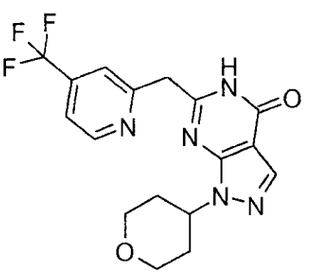
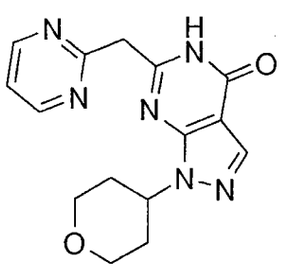
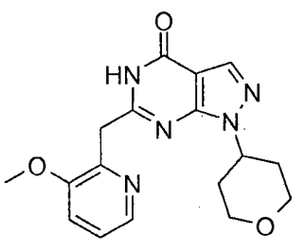
40-1	
40-2	
40-3	
40-4	
40-5	

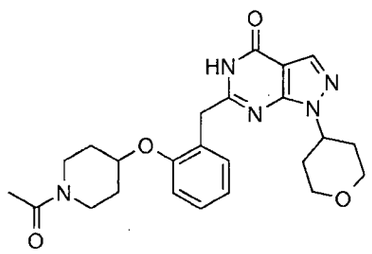
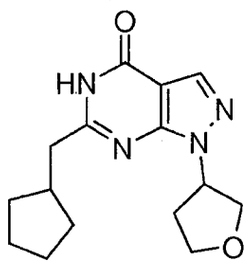
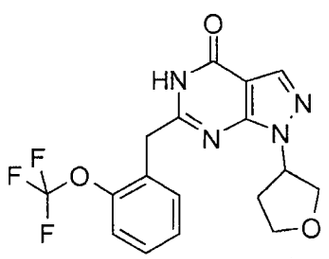
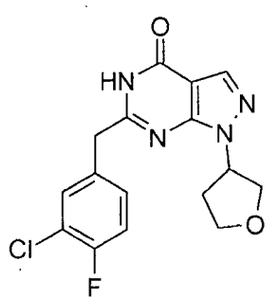
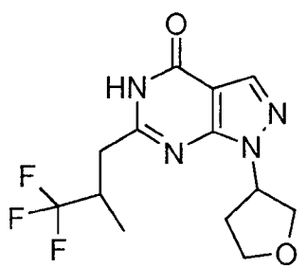
40-6	
40-7	
41	
42	
43	

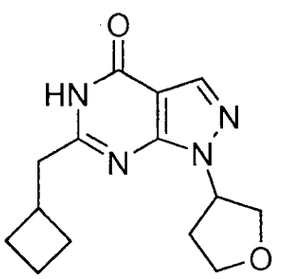
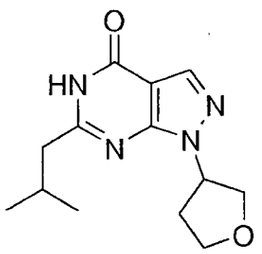
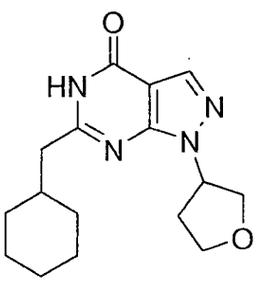
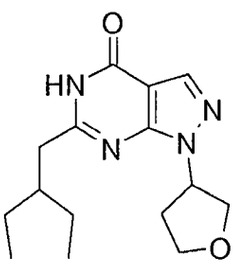
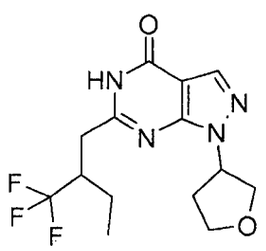
44	
45	
46 & 131 & 132	
47	
48	

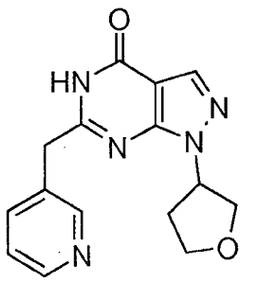
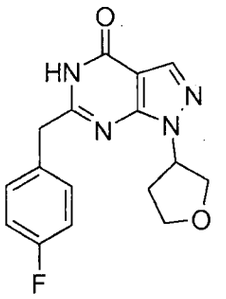
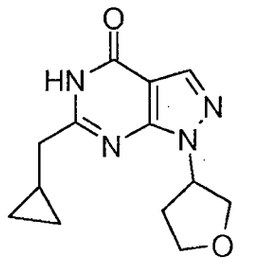
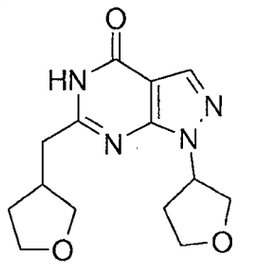
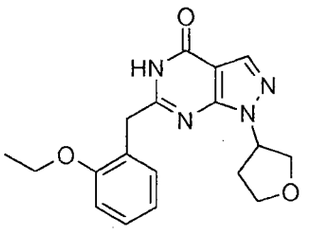
49	
50	
51	
52	
53	

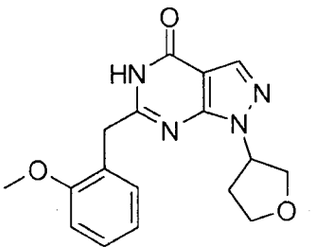
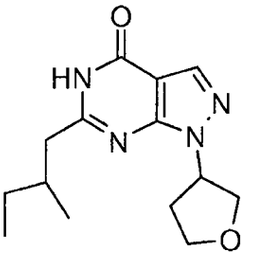
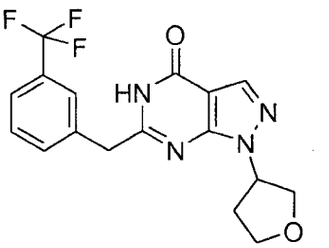
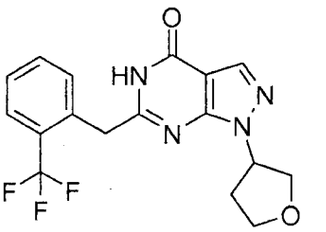
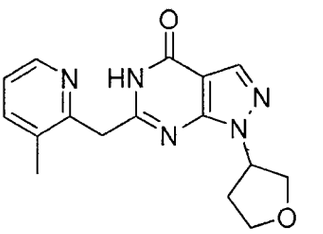
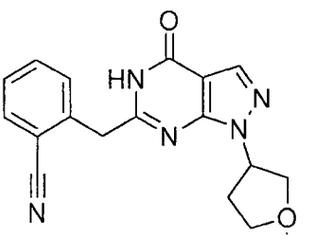
54	
55	
56	
57 & 58	
60	
61 & 62	

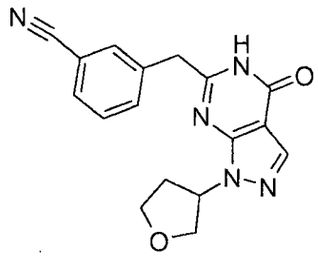
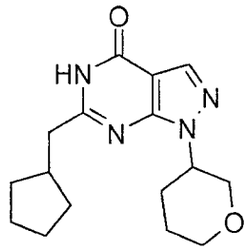
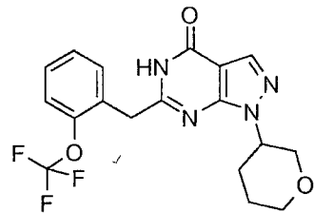
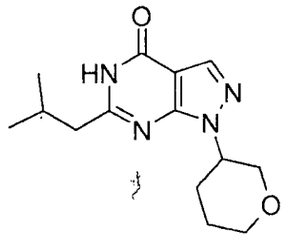
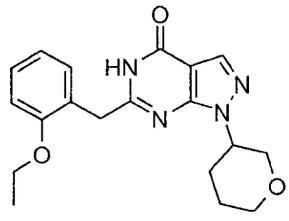
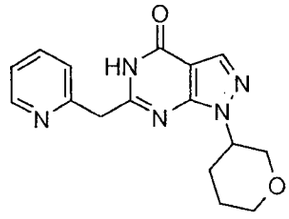
63	
64	
65	
66	
67	

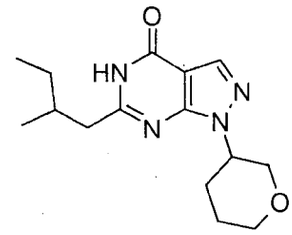
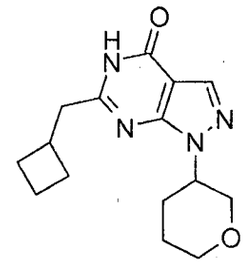
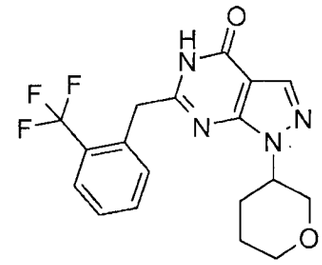
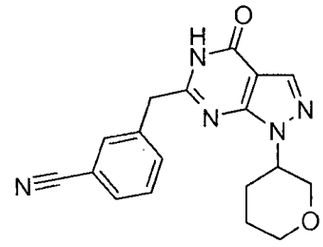
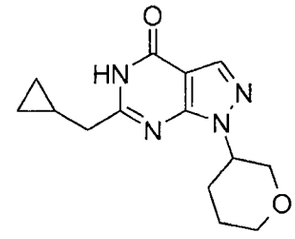
68	
69	
70	
71	
72	

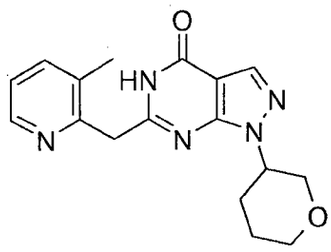
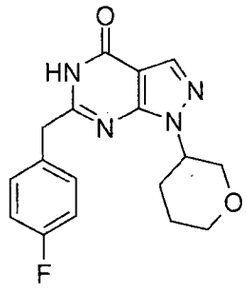
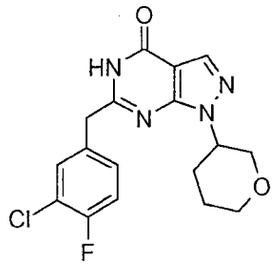
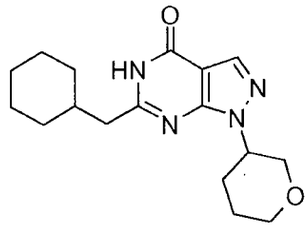
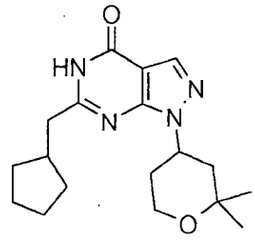
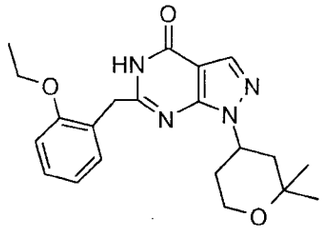
73	
74 & 132-3 & 132-4	
75	
76	
77	

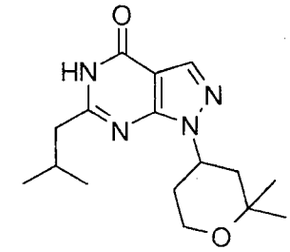
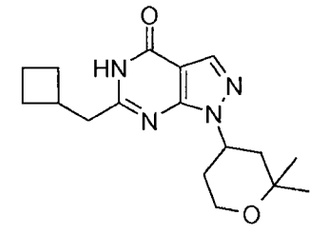
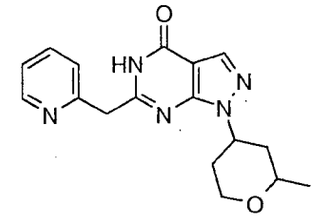
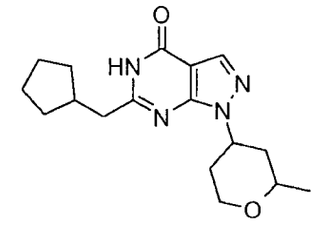
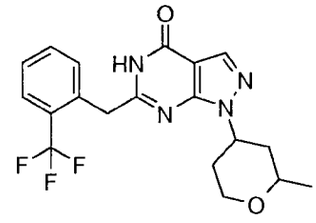
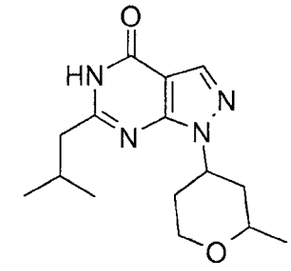
78	
79	
80	
81	
82	

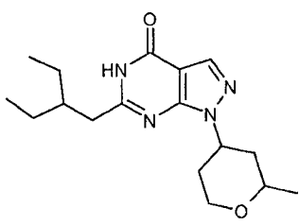
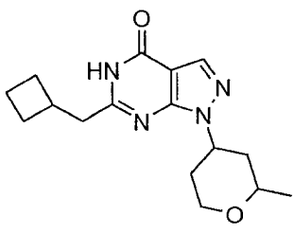
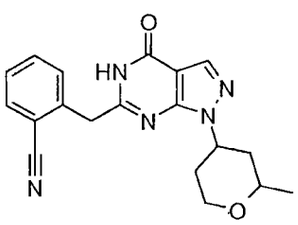
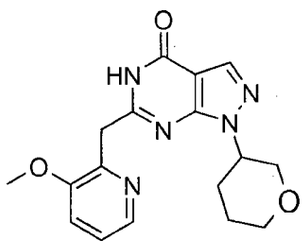
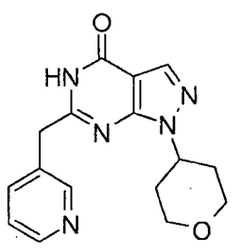
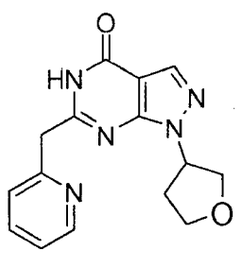
83	
84	
85	
86	
87	
88	

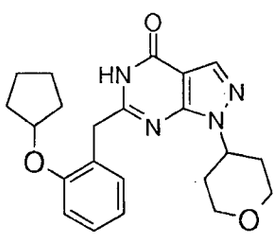
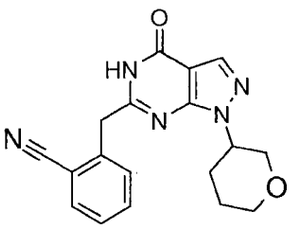
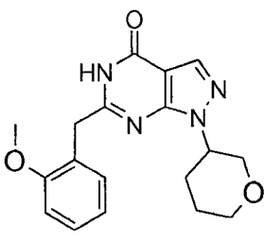
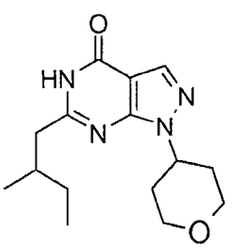
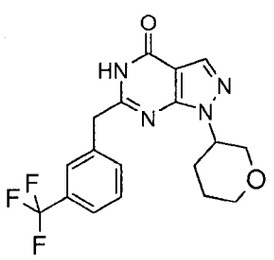
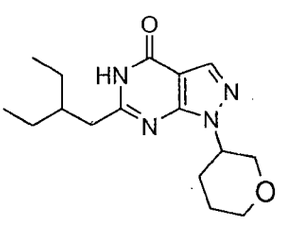
89	
90	
91	
92	
93	
94	

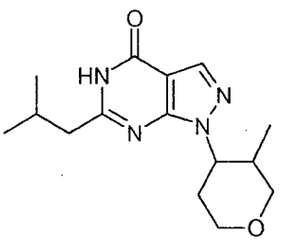
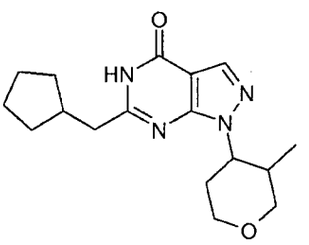
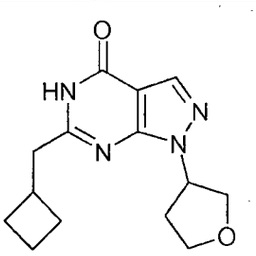
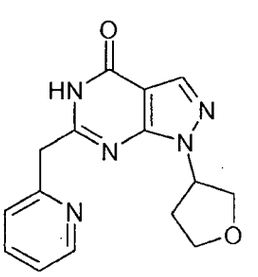
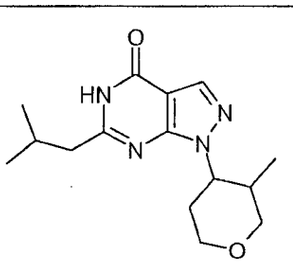
95	
96	
97	
98	
99	

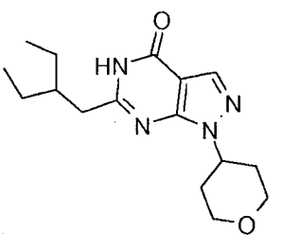
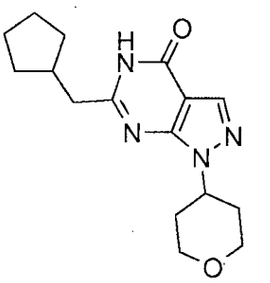
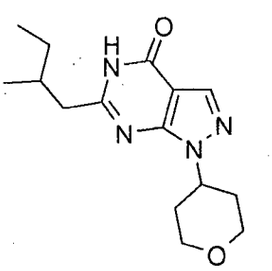
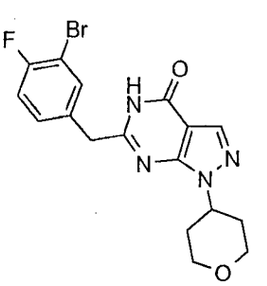
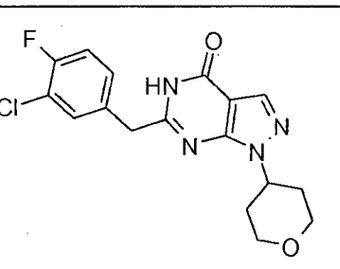
100	
101	
102	
103	
104	
105	

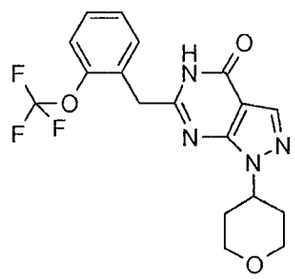
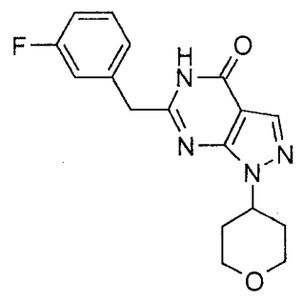
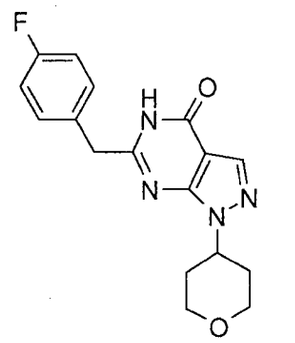
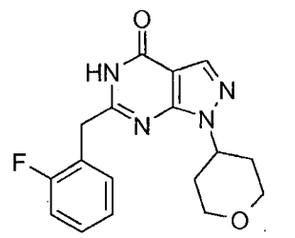
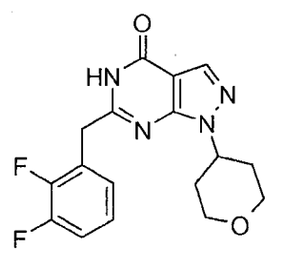
106	
108	
111 & 118	
112 & 117	
113 & 116	
114 & 115	

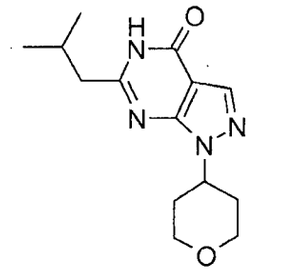
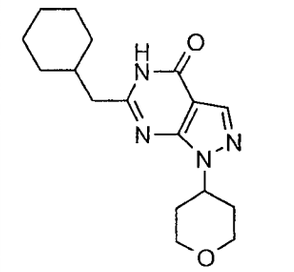
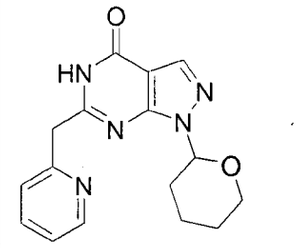
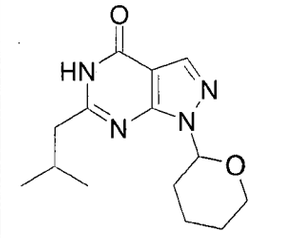
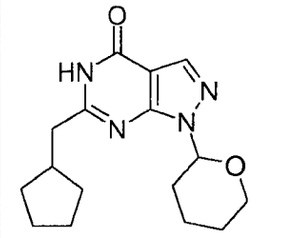
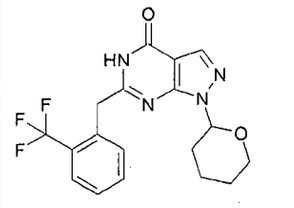
119	
120	
121	
122	
123	
124	

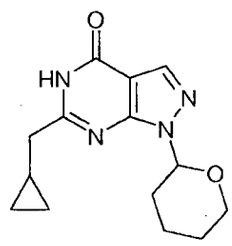
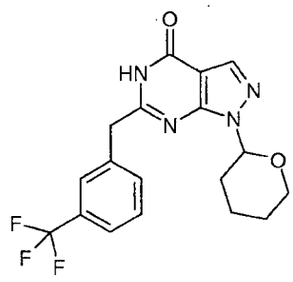
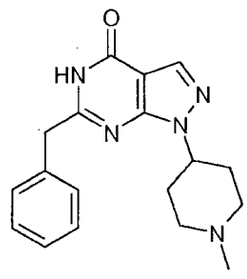
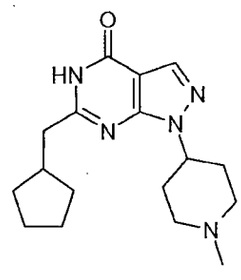
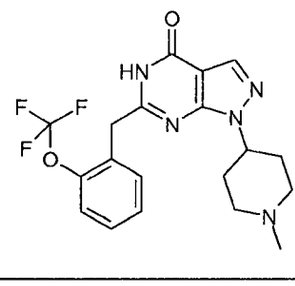
125	
126	
127	
128	
129	
130	

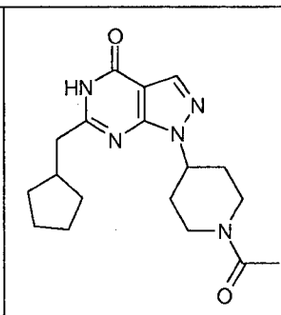
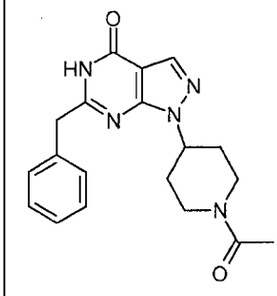
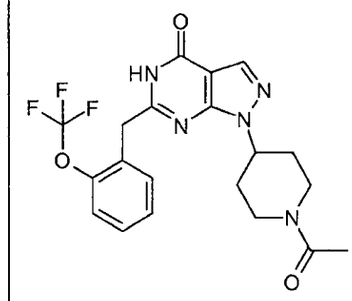
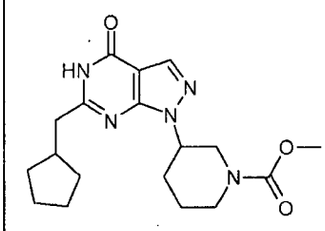
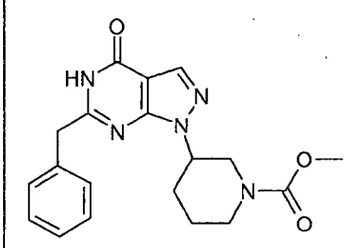
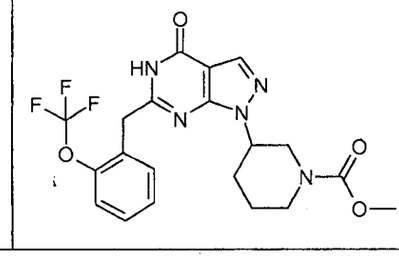
132-1	
132-2 & 132-5	
132-6 & 132-9	
132-7	
132-8	

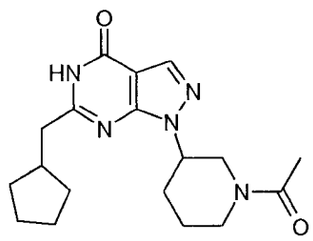
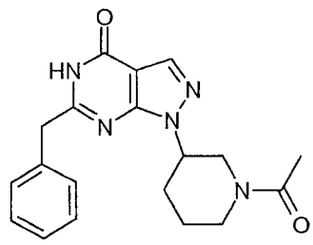
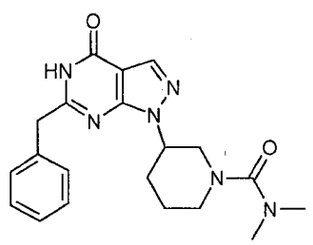
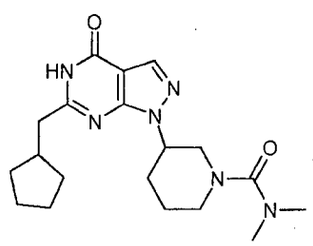
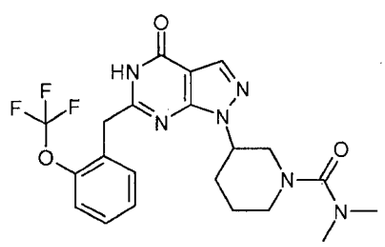
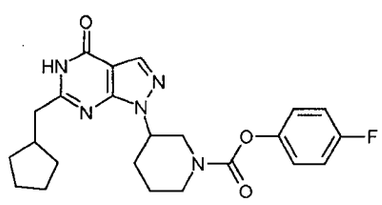
133	
134	
135	
136	
137	

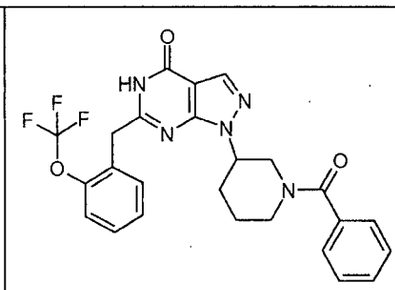
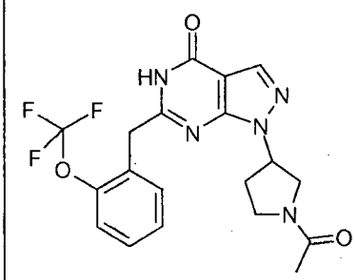
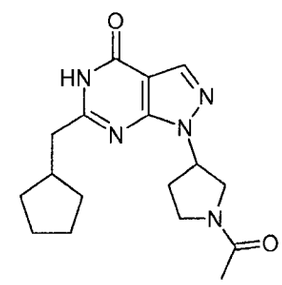
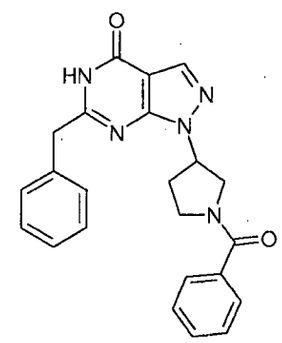
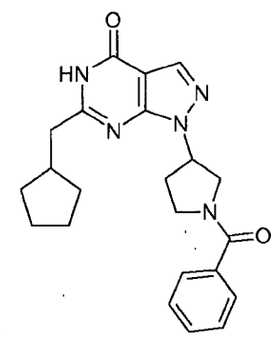
138	
139	
140	
141	
142	

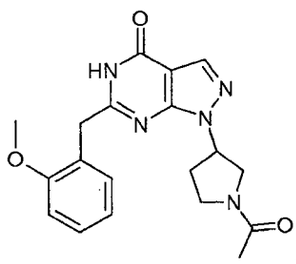
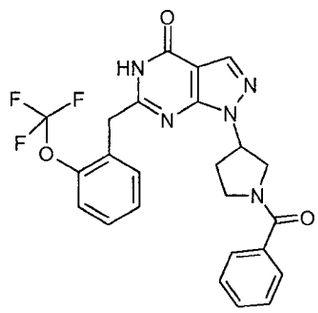
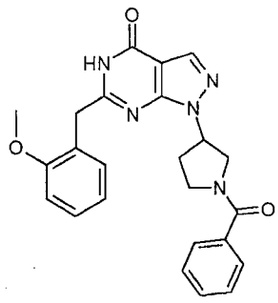
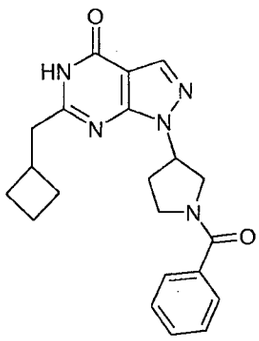
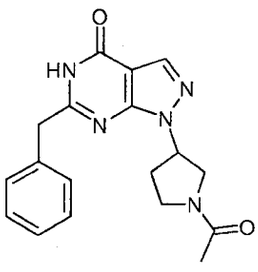
143	
144	
145	
146	
147	
147-1	

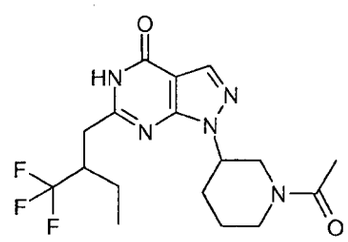
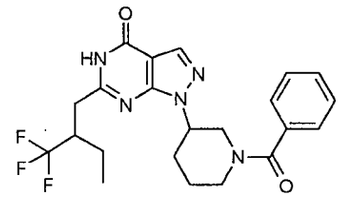
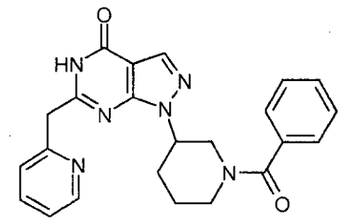
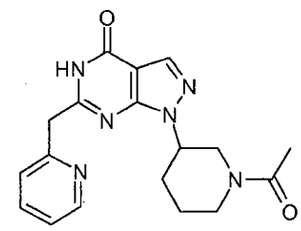
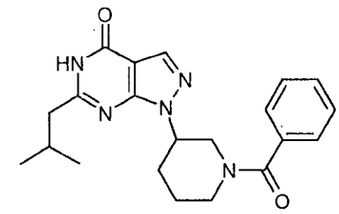
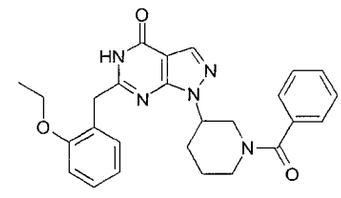
147-2	
147-3	
148	
149	
150	

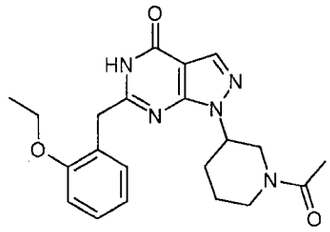
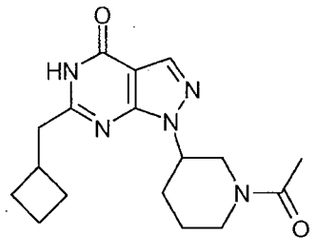
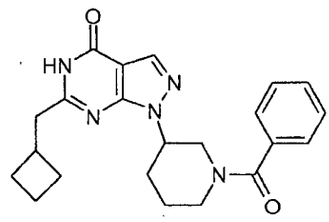
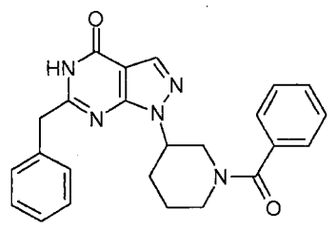
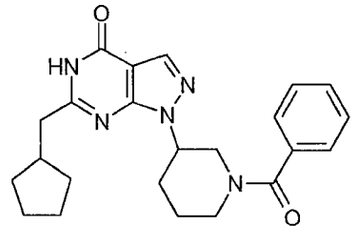
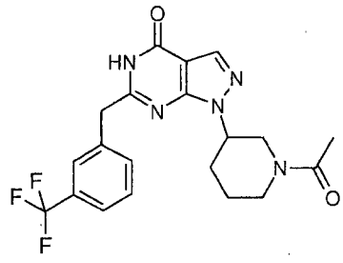
151	
152	
153	
154	
155	
156	

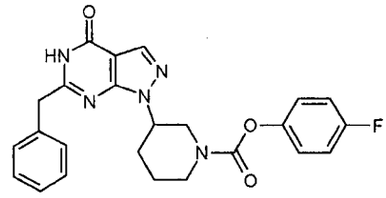
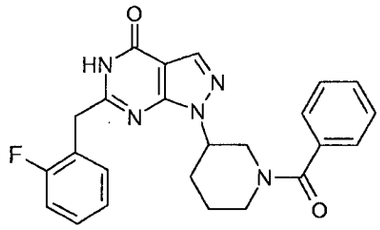
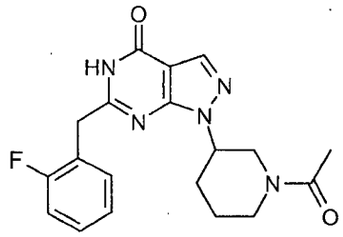
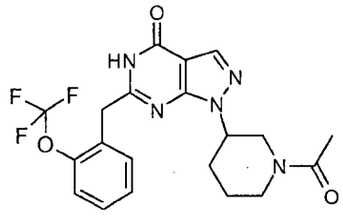
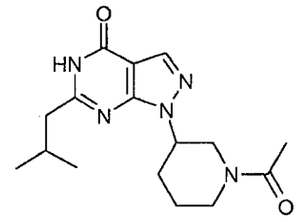
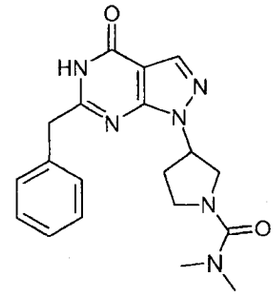
157	
158	
159	
160	
161	
162	

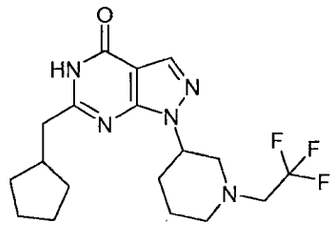
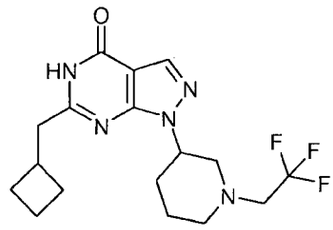
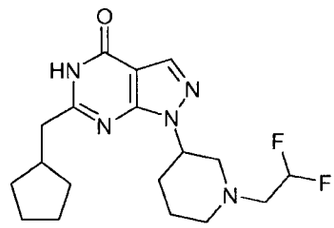
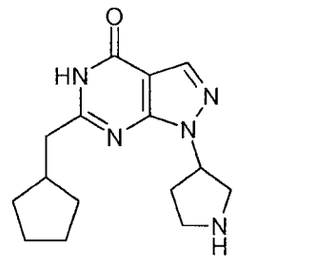
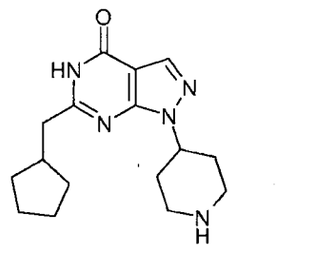
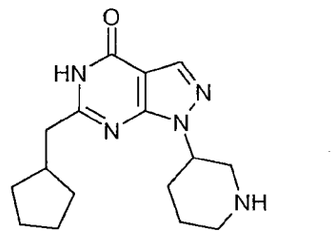
163	
164	
165	
166	
167	

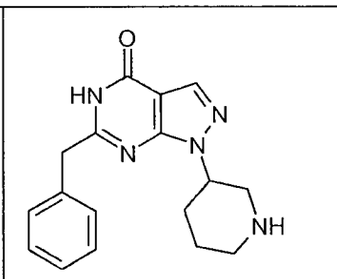
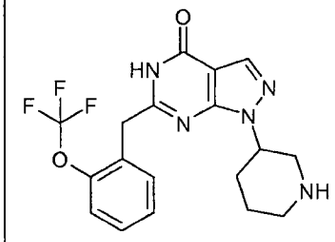
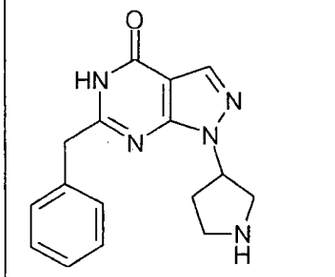
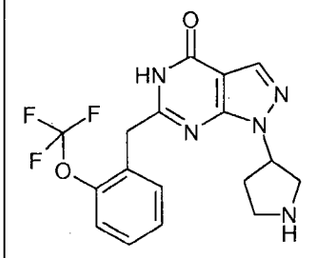
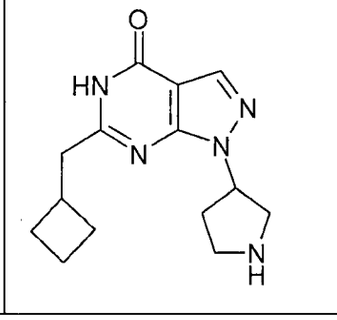
168	
169	
170	
171	
172	

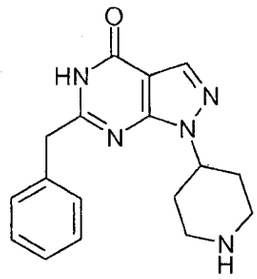
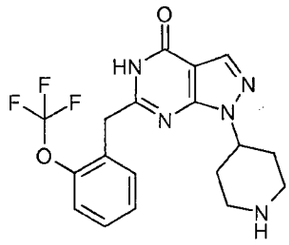
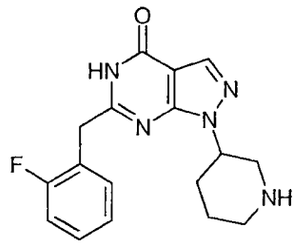
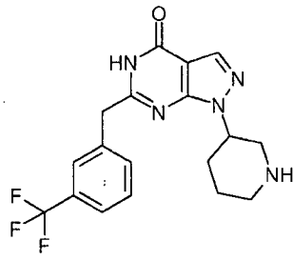
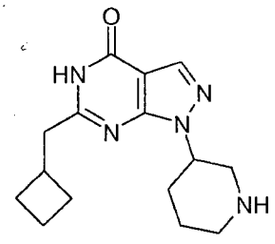
173	
174	
175	
176	
177	
178	

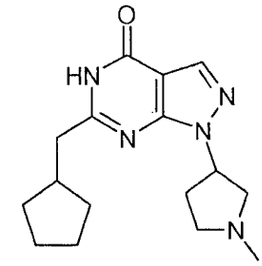
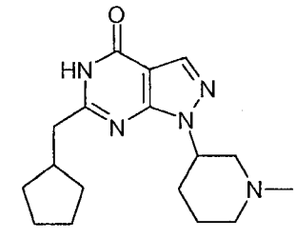
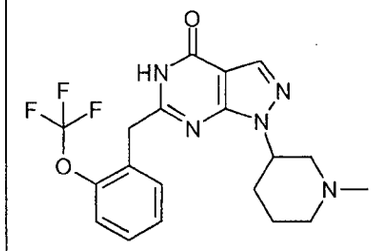
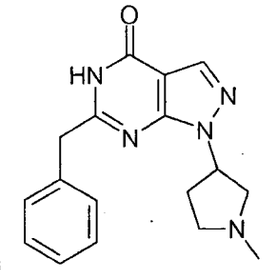
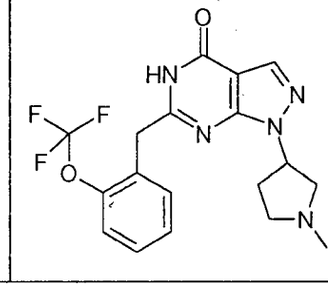
179	
180	
181	
182	
183	
184	

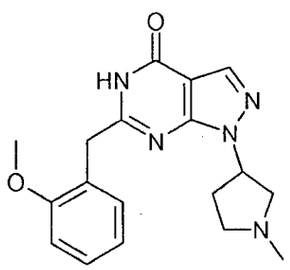
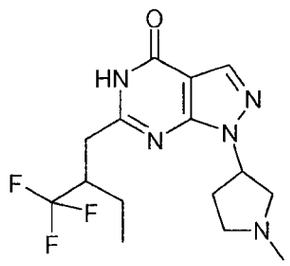
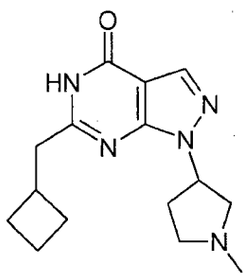
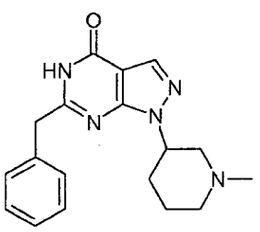
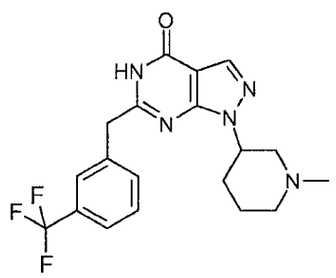
185	
186	
187	
188	
189	
190	

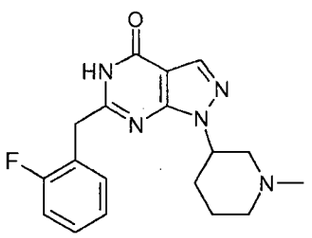
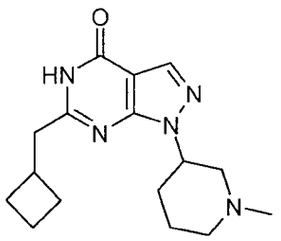
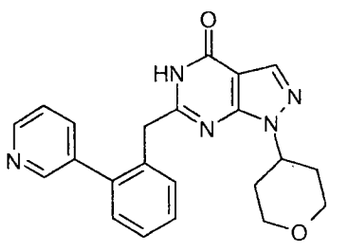
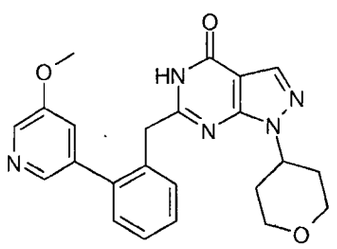
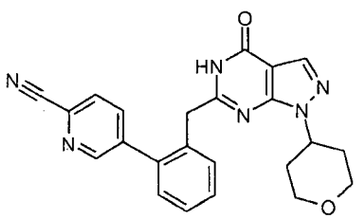
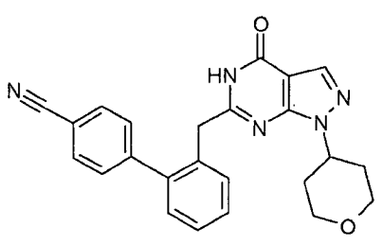
191,	
192	
193	
194	
195	
196	

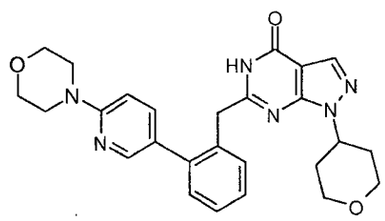
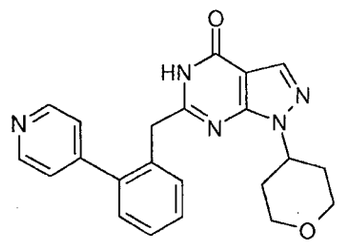
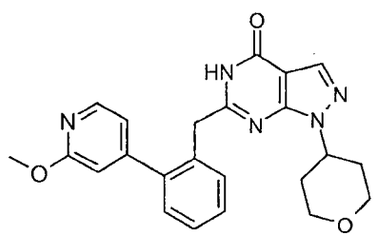
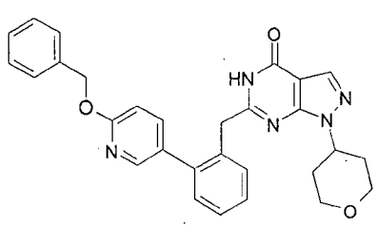
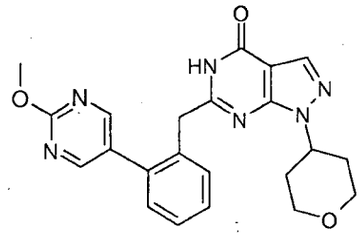
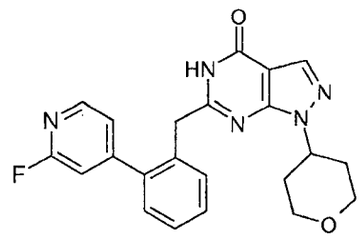
197	
198	
199	
200	
201	

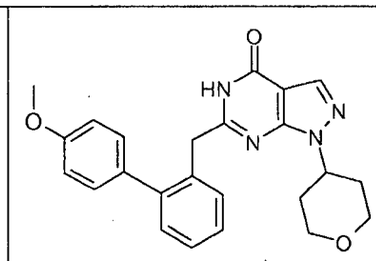
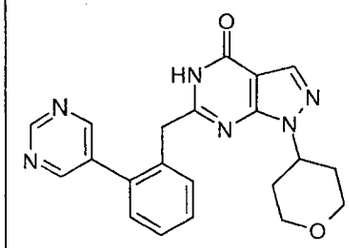
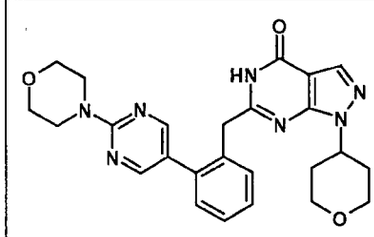
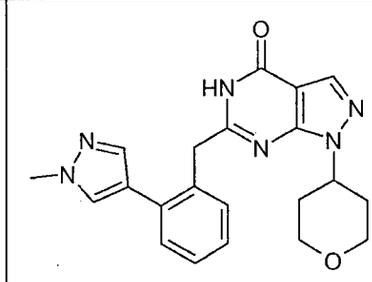
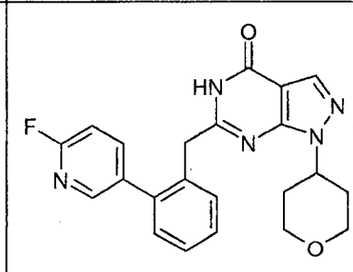
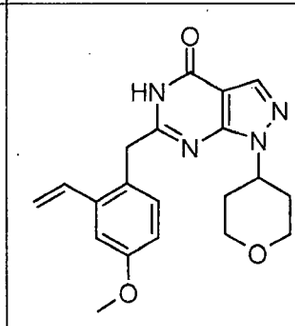
202	
203	
204	
205	
206	

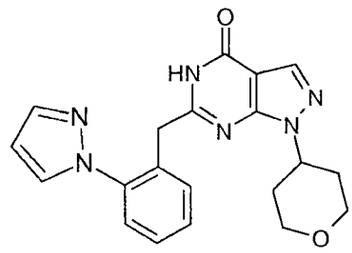
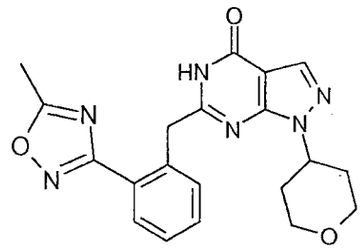
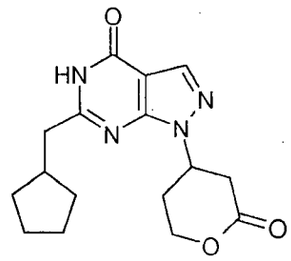
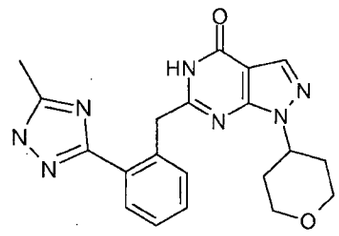
207	
208	
209	
210	
211	

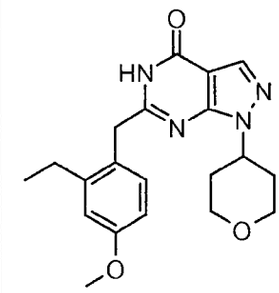
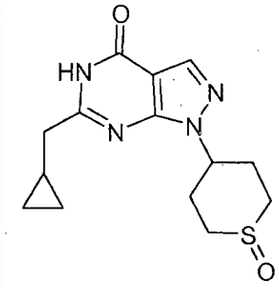
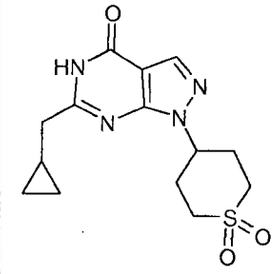
212	
213	
214	
215	
216	

217	
218	
219	
220	
221	
222	

223	
224	
225	
226	
227	
228	

229	
230	
230-1	
230-2	
230-3	
230-4	

231	
232	
233	
234	

235	
236	
237	

These 18 main aspects of the inventions, subgroups thereof and some further other aspects of the invention are listed as elements of the following matrix 0 and matrix I which make reference to the notation ($\underline{Hc}^{i}\ R^{1.j}\ R^{2.k}\ R^{3.l}\ R^{4/5.m}\ R^{10.n}$), the reading of which is as defined above, i.e. together with general formula I and the remaining features like x, y, as outlined directly below said matrix 0 or matrix I.

Matrix 0 and matrix I show in the right hand column the embodiments ($\underline{Hc}^{i}$ $R^{1.j}$ $R^{2.k}$ $R^{3.l}$ $R^{4/5.m}$ $R^{10.n}$) of the invention according to general formula I that are considered preferred, independent and separable of each other, i.e. individual aspects of the invention. The left hand column provides a reference number to such embodiments. The embodiments or elements are listed in the order from less preferred to most preferred, the preference of the embodiments is ascending with the reference number. This means that the embodiment, which is presented by the matrix element in the last row, last entry of matrix 0 or matrix I is the most preferred embodiment, while the embodiments of matrix I are preferred over the embodiments of matrix 0.

Aspects 1 to 18 are the main aspects of the invention.

Matrix 0

The first embodiment of this matrix 0 represents the first general aspect of the invention. The following embodiments are subsets thereof.

No.	Embodiment
M0-001	$\underline{Hc}^{1}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-002	$\underline{Hc}^{2}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-003	$\underline{Hc}^{2}R^{1.0.2}R^{2.3}R^{3.3}R^{4/5.2}R^{10.0.2}$
M0-004	$\underline{Hc}^{3}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.0.3}$
M0-005	$\underline{Hc}^{3}R^{1.0.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.0.3}$
M0-006	$\underline{Hc}^{7.0}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-007	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.1}R^{3.1}R^{4/5.2}R^{10.0.2}$
M0-008	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-009	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-010	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.4}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-011	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-012	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-013	$\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-014	$\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-015	$\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-016	$\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$
M0-017	$\underline{Hc}^{7.0}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-018	$\underline{Hc}^{7.1}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-019	$\underline{Hc}^{7.1}R^{1.0.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-020	$\underline{Hc}^{7.1}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-021	$\underline{Hc}^{7.1}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$

M0-022	$\underline{Hc}^{7.1}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-023	$\underline{Hc}^{7.1}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-024	$\underline{Hc}^{7.1}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-025	$\underline{Hc}^{7.1}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$
M0-026	$\underline{Hc}^{7.1}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-027	$\underline{Hc}^{7.1}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$
M0-028	$\underline{Hc}^{8}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-029	$\underline{Hc}^{8}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-030	$\underline{Hc}^{8}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-031	$\underline{Hc}^{8}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-032	$\underline{Hc}^{8}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-033	$\underline{Hc}^{8}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-034	$\underline{Hc}^{8}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-035	$\underline{Hc}^{8}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$
M0-036	$\underline{Hc}^{8}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-037	$\underline{Hc}^{8}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$
M0-038	$\underline{Hc}^{9}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-039	$\underline{Hc}^{9}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-040	$\underline{Hc}^{9}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-041	$\underline{Hc}^{9}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-042	$\underline{Hc}^{9}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-043	$\underline{Hc}^{9}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-044	$\underline{Hc}^{9}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-045	$\underline{Hc}^{9}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$
M0-046	$\underline{Hc}^{9}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-047	$\underline{Hc}^{9}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$
M0-048	$\underline{Hc}^{9}R^{1.4}R^{2.4}R^{3.2}R^{4/5.2}R^{10.4}$
M0-049	$\underline{Hc}^{9}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
M0-050	$\underline{Hc}^{9}R^{1.4}R^{2.4}R^{3.3}R^{4/5.2}R^{10.4}$
M0-051	$\underline{Hc}^{9}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
M0-052	$\underline{Hc}^{10}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-053	$\underline{Hc}^{10}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-054	$\underline{Hc}^{10}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-055	$\underline{Hc}^{10}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-056	$\underline{Hc}^{10}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-057	$\underline{Hc}^{10}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-058	$\underline{Hc}^{10}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-059	$\underline{Hc}^{10}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$
M0-060	$\underline{Hc}^{10}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-061	$\underline{Hc}^{10}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$
M0-062	$\underline{Hc}^{10}R^{1.4}R^{2.4}R^{3.2}R^{4/5.2}$
M0-063	$\underline{Hc}^{10}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}$
M0-064	$\underline{Hc}^{10}R^{1.4}R^{2.4}R^{3.3}R^{4/5.2}$
M0-065	$\underline{Hc}^{10}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-066	$\underline{Hc}^{10}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$

whereby for each matrix embodiment of matrix 0:

x independently from each other = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2; preferably being 0 or 1, more preferably x= 0:

y independently from each other y = 0, or 1; more preferably y= 0, whereby specific definitions with the embodiments of the matrix prevail;

and pharmaceutically acceptable salts and/or solvates thereof.

and with the proviso - for each embodiment of matrix 0 for that this proviso is applicable - such as for embodiments which comprise ***Hc*** as defined by $\underline{Hc}^1$ or $\underline{Hc}^3$ - that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ spacer.

It will be evident, that if x and/or y = 0 then ***Hc*** is unsubstituted, i. e. the corresponding valences of the ring member atoms are saturated by hydrogen.

In case R^{10} is not sufficiently defined in matrix 0 it shall be $R^{10.0.4}$ or $R^{10.0.5}$, preferably $R^{10.0.5}$.

matrix I:

No.	Embodiment
MI-001	$\underline{Hc}^1R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-002	$\underline{Hc}^2R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-003	$\underline{Hc}^2R^{1.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.2}$
MI-004	$\underline{Hc}^2R^{1.2}R^{2.3}R^{3.3}R^{4/5.2}R^{10.2}$
MI-005	$\underline{Hc}^3R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-006	$\underline{Hc}^3R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-007	$\underline{Hc}^3R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-008	$\underline{Hc}^3R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-009	$\underline{Hc}^3R^{1.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-010	$\underline{Hc}^3R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$

MI-011	$\underline{Hc}^{3}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-012	$\underline{Hc}^{3}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$
MI-013	$\underline{Hc}^{3}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-014	$\underline{Hc}^{3}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-015	$\underline{Hc}^{3}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-016	$\underline{Hc}^{3}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-017	$\underline{Hc}^{3}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-018	$\underline{Hc}^{3}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$
MI-019	$\underline{Hc}^{3}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$
MI-020	$\underline{Hc}^{3}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-021	$\underline{Hc}^{3}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-022	$\underline{Hc}^{3}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-023	$\underline{Hc}^{3}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-024	$\underline{Hc}^{3}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-025	$\underline{Hc}^{3}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$
MI-026	$\underline{Hc}^{3}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$
MI-027	$\underline{Hc}^{4}R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-028	$\underline{Hc}^{4}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-029	$\underline{Hc}^{4}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-030	$\underline{Hc}^{4}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-031	$\underline{Hc}^{4}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-032	$\underline{Hc}^{4}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-033	$\underline{Hc}^{4}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-034	$\underline{Hc}^{4}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-035	$\underline{Hc}^{4}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-036	$\underline{Hc}^{4}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-037	$\underline{Hc}^{4}R^{1.2}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-038	$\underline{Hc}^{4}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-039	$\underline{Hc}^{4}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$
MI-040	$\underline{Hc}^{4}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-041	$\underline{Hc}^{4}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-042	$\underline{Hc}^{4}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-043	$\underline{Hc}^{4}R^{1.3}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-044	$\underline{Hc}^{4}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-045	$\underline{Hc}^{4}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-046	$\underline{Hc}^{4}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$
MI-047	$\underline{Hc}^{4}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$
MI-048	$\underline{Hc}^{4}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-049	$\underline{Hc}^{4}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-050	$\underline{Hc}^{4}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-051	$\underline{Hc}^{4}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-052	$\underline{Hc}^{4}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-053	$\underline{Hc}^{4}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$
MI-054	$\underline{Hc}^{4}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$
MI-055	$\underline{Hc}^{7.1}R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-056	$\underline{Hc}^{7.1}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$

MI-057	$\underline{Hc}^{7.1}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-058	$\underline{Hc}^{7.1}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-059	$\underline{Hc}^{7.1}R^{1.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-060	$\underline{Hc}^{7.1}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-061	$\underline{Hc}^{7.1}R^{1.2}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-062	$\underline{Hc}^{7.1}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-063	$\underline{Hc}^{7.1}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$
MI-064	$\underline{Hc}^{7.1}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-065	$\underline{Hc}^{7.1}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-066	$\underline{Hc}^{7.1}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-067	$\underline{Hc}^{7.1}R^{1.3}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-068	$\underline{Hc}^{7.1}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-069	$\underline{Hc}^{7.1}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-070	$\underline{Hc}^{7.1}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$
MI-071	$\underline{Hc}^{7.1}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$
MI-072	$\underline{Hc}^{7.1}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-073	$\underline{Hc}^{7.1}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-074	$\underline{Hc}^{7.1}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-075	$\underline{Hc}^{7.1}R^{1.4}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-076	$\underline{Hc}^{7.1}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-077	$\underline{Hc}^{7.1}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-078	$\underline{Hc}^{7.1}R^{1.4}R^{2.5}R^{3.2}R^{4/5.34}$
MI-079	$\underline{Hc}^{7.1}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$

MI-080	$\underline{Hc}^{8}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-081	$\underline{Hc}^{8}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-082	$\underline{Hc}^{8}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-083	$\underline{Hc}^{8}R^{1.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-084	$\underline{Hc}^{8}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-085	$\underline{Hc}^{8}R^{1.2}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-086	$\underline{Hc}^{8}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-087	$\underline{Hc}^{8}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$
MI-088	$\underline{Hc}^{8}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-089	$\underline{Hc}^{8}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-090	$\underline{Hc}^{8}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-091	$\underline{Hc}^{8}R^{1.3}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-092	$\underline{Hc}^{8}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-093	$\underline{Hc}^{8}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-094	$\underline{Hc}^{8}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$
MI-095	$\underline{Hc}^{8}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$
MI-096	$\underline{Hc}^{8}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-097	$\underline{Hc}^{8}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-098	$\underline{Hc}^{8}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-099	$\underline{Hc}^{8}R^{1.4}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-100	$\underline{Hc}^{8}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-101	$\underline{Hc}^{8}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-102	$\underline{Hc}^{8}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$

MI-103	$\underline{Hc}^{8}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$

whereby for each embodiment of matrix I:

x independently from each other = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2;

y independently from each other y = 0 or 1;

and pharmaceutically acceptable salts and/or solvates thereof

and with the proviso - for each embodiment of matrix 0 for that this proviso is applicable - such as for embodiments which comprise ***Hc*** as defined by $\underline{Hc}^{1}$ or $\underline{Hc}^{3}$ - that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ spacer.

It will be evident, that if x and/or y = 0 then ***Hc*** is unsubstituted, i. e. the corresponding valences of the ring member atoms are saturated by hydrogen.

In case R^{10} is not sufficiently defined in matrix I it shall be $R^{10.4}$.

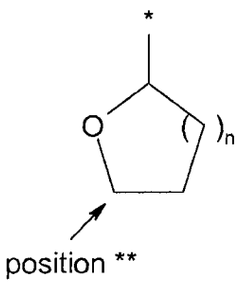
Additional embodiments according to the invention and subset of the aspects 1 to 17 and the embodiments of matrix 0 or matrix I

In the following further embodiments of the invention are presented. Each one is independent and separable, i.e. individual aspect of the invention.

Additionally mentioned are the embodiments ($\underline{Hc}^{5}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$) and ($\underline{Hc}^{6}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$), with the remaining features as outlined for the elements of matrix I.

a.) subset of aspects 1 – 17 and embodiments of matrix 0 or I with respect to R^2

(a.1.1) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** within the group $Hc[R^2]_x[R^3]_y$ may be a group defined by the following formula D1

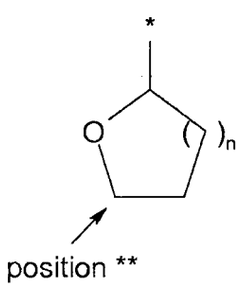


(D1),

whereby the * is the attachment point to the pyrazolo-group in general formula I and n = 0, 1, 2 or 3, except that in this subset for no embodiment at the position ** there is an R^2 that comprises a $-CH_2-$ group by which R^2 is bound at said position **:

This subset is called "subset a.1.1".

(a.1.2) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** within the group $Hc[R^2]_x[R^3]_y$ may be a group defined by the following formula D1

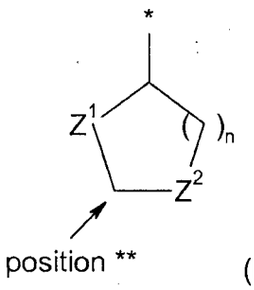


(D1),

whereby the * is the attachment point to the pyrazolo-group in general formula I and n = 0, 1, 2 or 3; except that in this subset for no embodiment at the position ** there is an R^2 or R^3 other than H.

This subset is called "subset a.1.2".

(a.2.1) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** within the group $\underline{Hc}[R^2]_x[R^3]_y$ may be a group defined by the following formula D1-2



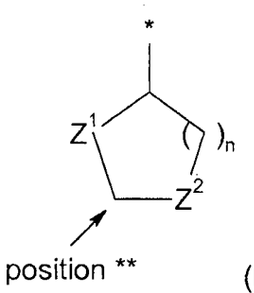
(D1-2),

whereby the * is the attachment point to the pyrazolo-group in general formula I and n = 1, 2 or 3 and wherein Z^1 is selected from the group of N, O and $S(O)_r$, with r = 0, 1, 2 and Z^2 is selected from the group of C, N, O and $S(O)_r$, with r = 0, 1, 2, in all cases with eventually remaining valences of Z^1 or Z^2 being saturated by H or as the case may be by R^2 or R^3,

except that within this subset for no embodiment at the position ** there is an R^2 that comprises an optionally substituted $-CH_2-$ group by which this R^2 is bound at said position **:

This subset is called "subset a.2.1".

(a.2.2) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** within the group $\underline{Hc}[R^2]_x[R^3]_y$ may be a group defined by the following formula D1-2



(D1-2),

whereby the * is the attachment point to the pyrazolo-group in general formula I and n = 1, 2 or 3 and wherein Z^1 is selected from the group of N, O and $S(O)_r$, with r = 0, 1, 2 and Z^2 is selected from the group of C, N, O and $S(O)_r$, with r = 0, 1, 2, in all cases with eventually remaining valences of Z^1 or Z^2 being saturated by H or as the case may be by R^2 or R^3,

except that within this subset for no embodiment at the position ** there is an R^2 or R^3 other than H:

This subset is called "subset a.2.2".

(a.3) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrofuranyl, except that within this subset for no embodiment R^2 is a CH_3-group that is bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.3".

(a.4) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrofuranyl, except that within this subset for no embodiment R^2 is a R^{10}-O- C_{2-6}-alkyl-group having a CH_2-group by which it is bound to a C-atom of the tetrahydrofuranyl, which is at the alpha position to the ring oxygen atom.
This subset is called "subset a.4".

(a.5.1) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrofuranyl, except that within this subset for no embodiment R^2 is a C_{1-6}-alkyl-group being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.5.1".

(a.5.2) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrofuranyl, except that within this subset for no embodiment R^2 is a C_{2-6}-alkenyl-group-being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.5.2".

(a.5.3) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrofuranyl, except that in this subset for no embodiment R^2 is a C_{2-6}-alkynyl-group-being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.5.3".

(a.6) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrothiophenyl, except that in this subset for no embodiment R^2 is a CH_3-group being bound at the alpha position to the ring sulphur atom.
This subset is called "subset a.6".

(a.7) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrothiophenyl, except that in this subset for no embodiment R^2 is a R^{10}-O- C_{2-6}-alkyl-group having a CH_2-group by which it is bound to a C-atom of the tetrahydrothiophenyl, which is at the alpha position to the ring sulphur atom.
This subset is called "subset a.7".

(a.8) In one individual and independent subset of embodiments according to the present invention the embodiments correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrothiophenyl, except that in this subset for no embodiment R^2 is a C_1-

$_6$-alkyl-group having a CH_2-group by which it is bound at the alpha position to the ring sulphur atom.
This subset is called "subset a.8".

(a.9) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydropyranyl or a tetrahydrothiopyranyl, except that in this subset for no embodiment R^2 is a CH_3-group being bound to the alpha position of the ring oxygen atom or the sulphur atom respectively.
This subset is called "subset a.9".

(a.10) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydropyranyl or a tetrahydrothiopyranyl, except that in this subset for no embodiment R^2 is a R^{10}-O-C_{2-6}-alkyl-group having a CH_2-group by which it is bound to a C-atom of the tetrahydropyranyl or tetrahydrothiopyranyl which C-atom is at the alpha position to the ring oxygen atom or the sulphur atom respectively.
This subset is called "subset a.10".

(a.11) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydropyranyl or a tetrahydrothiopyranyl, except that in this subset for no embodiment R^2 is a C_{1-6}-alkyl-group having a CH_2-group by which it is bound at the alpha position to the ring oxygen atom or the sulphur atom respectively.
This subset is called "subset a.11".

(a.12) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** may be an

oxetanyl group, except that in this subset for no embodiment ***Hc*** is an oxetanyl-group.
This subset is called "subset a.12".

(a.13) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be a cyclic hexanosyl sugar group in which for any of the hydroxy groups the hydrogen optionally may be replaced by any other group and / or ***Hc*** is or may be a cyclic mono-desoxy or di-desoxy hexanosyl sugar group in which for any of the remaining hydroxy groups the hydrogen optionally may be replaced by any other group, except that in this subset for no embodiment R^2 is a CH_3-group being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.13".

(a.14) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be a cyclic hexanosyl sugar group in which for any of the hydroxy groups the hydrogen optionally may be replaced by any other group and / or ***Hc*** is or may be a cyclic mono-desoxy or di-desoxy hexanosyl sugar group in which for any of the remaining hydroxy groups the hydrogen optionally may be replaced by any other group, except that in this subset for no embodiment R^2 is a C_{1-6}-alkyl-group being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.14".

(a.15) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be a cyclic hexanosyl sugar group in which for any of the hydroxy groups the hydrogen optionally may be replaced by any other group and / or ***Hc*** is or may be a cyclic mono-desoxy or di-desoxy hexanosyl sugar group in which for any of the remaining hydroxy groups the hydrogen optionally may be replaced by any other

group, except that in this subset for no embodiment R^2 is a R^{10}-O-C_{2-6}-alkyl- group being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.15".

(a.16) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 or I in which R^2 is defined such that it may comprise a group selected from $(R^{10})_2N$- and $(R^{10})_2N$-C_{1-3}-alkyl-, except that in this subset for no embodiment R^2 shall be $(R^{10})_2N$- or $(R^{10})_2N$-C_{1-3}-alkyl-, while all remaining definitions of R^2 remain unchanged.
This subset is called "subset a.16".

b.) subset of embodiments of matrix 0 or matrix I with respect to $R^{4/5}$

(b.1) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of the embodiments of matrix 0 or matrix I in which $\mathbf{R^{4/5}}$ is $\mathbf{R^{4/5.2}}$, whereby for the embodiments of this subset

$\mathbf{R^{4/5.2-2}}$ shall mean that $\mathbf{R^4}$ and $\mathbf{R^5}$ independently of one another are H- or fluorine.

This subset is called "subset b.1".

c.) subset of embodiments of matrix I with respect to R^{10}

(c.1) In one individual and independent subset of embodiments according to the present invention concerns each embodiment selected from the group of matrix I with $\mathbf{R^{10}}$ being defined by $\mathbf{R^{10.2}}$, $\mathbf{R^{10.3}}$or $\mathbf{R^{10.4}}$: for the embodiments of this subset each of the definitions $\mathbf{R^{10.2}}$, $\mathbf{R^{10.3}}$and $\mathbf{R^{10.4}}$ is extended so that $\mathbf{R^{10}}$ also may be H, in case this $\mathbf{R^{10}}$ is bound to a nitrogen atom.
This subset is called "subset c.1".

It will be evident that the subsets as defined under a.) and b.) within this section "Additional embodiments according to the invention / subset of aspects 1 – 17 and

the embodiments of matrix 0 or matrix I" correspond with embodiments of aspects 1 – 17 and matrix 0, matrix I respectively, whereby the scope of specific definitions is changed. In case these changes are limitations the new definitions can be considered to include provisos. Therefore these embodiments are considered to be only "subsets" of aspects 1 – 17 and the embodiments of matrix 0, matrix I respectively.

Each embodiment of general formula I defined by aspects 1 – 18 and any of the elements of matrix 0, matrix I, or each embodiment defined by the above subsets a.), b.) or c.) is considered an independent and separable aspect of the invention, i.e. an individual aspect of the invention.

USED TERMS AND DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by a person skilled in the art in light of the disclosure and the context. Examples include that specific substituents or atoms are presented with their 1 or 2 letter code, like H for hydrogen, N for nitrogen, C for carbon, O for oxygen, S for sulphur and the like. Optionally but not mandatorily the letter is followed by a hyphen to indicate a bond. As used in the specification, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_{1-6}-alkyl means an alkyl group or alkyl radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named group is the radical attachment point, for example, "thioalkyl" means a monovalent radical of the formula HS-alkyl-. If the term of a substituent starts or ends with a minus sign or hyphen, i.e. -. This sign emphasises the attachment point like in the aforementioned example HS-alkyl-, where the "alkyl" is linked to the group of which the HS-alkyl- is a substituent. Unless otherwise specified below, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups.

In general, all "**tautomeric forms and isomeric forms and mixtures**", whether individual geometric isomers or optical isomers or racemic or non-racemic mixtures of isomers, of a chemical structure or compound are intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure.

The term "**substituted**" as used herein explicitly or implicitly, means that any one or more hydrogen(s) on the designated atom is replaced with a member of the indicated group of substituents, provided that the designated atom's normal valence is not exceeded. In case a substituent is bound via a double bond, e.g. an oxo substituent, such substituent replaces two hydrogen atoms on the designated atom. The substitution shall result in a stable compound. "Stable" in this context preferably means a compound that from a pharmaceutical point of view is chemically and physically sufficiently stable in order to be used as an active pharmaceutical ingredient of a pharmaceutical composition.
If a substituent is not defined, it shall be hydrogen.

By the term "**optionally substituted**" is meant that either the corresponding group is substituted or it is not. Accordingly, in each occasion where this term is used, the non-substituted variation is a more pronounced aspect of the invention, i.e. preferably there are no such optional substituents.

The phrase "**pharmaceutically acceptable**" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "**pharmaceutically acceptable salt(s)**" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the

quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, and the like; and the salts prepared from organic acids such as acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, pamoic acid, maleic acid, hydroxymaleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, sulfanilic acid, 2-acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, methanesulfonic acid, ethane disulfonic acid, oxalic acid, isothionic acid, and the like. As the compounds of the present invention may have both, acid as well as basic groups, those compounds may therefore be present as internal salts too.

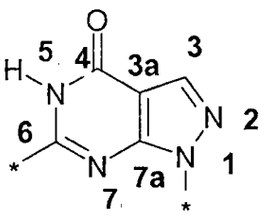
The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base form of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

"**Prodrugs**" are considered compounds that release an active parent drug of the present invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs according to the present invention are prepared by modifying functional groups present in the compound in such a way that these modifications are retransformed to the original functional groups under physiological conditions. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bound to any group that, when the prodrug of the present invention is administered to a mammalian subject, is retransformed to free said hydroxyl, amino, or sulfhydryl group. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

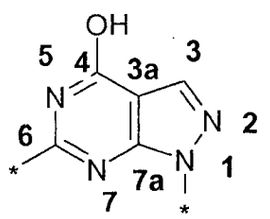
"**Metabolites**" are considered as derivatives of the compounds according to the present invention that are formed in vivo. Active metabolites are such metabolites that cause a pharmacological effect. It will be appreciated that metabolites of the compounds according to the present inventions are subject to the present invention as well, in particular active metabolites.

Some of the compounds may form "**solvates**". For the purposes of the invention the term "solvates" refers to those forms of the compounds which form, in the solid or liquid state, a complex by coordination with solvent molecules. Hydrates are a specific form of solvates in which the coordination takes place with water. According to the present invention, the term preferably is used for solid solvates, such as amorphous or more preferably crystalline solvates.

"**Scaffold**": The scaffold of the compounds according to the present invention is represented by the following core structure, the numeration of which is indicated in bold:

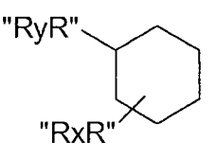


It will be evident for the skilled person in the art, that this scaffold can be described by its tautomeric "enol" form



In the context of the present invention both structural representations of the scaffold shall be considered the subject of the present invention, even if only one of the two representatives is presented. It is believed that for the majority of compounds under ambient conditions and therewith under conditions which are the relevant conditions for a pharmaceutical composition comprising said compounds, the equilibrium of the tautomeric forms lies on the side of the pyrazolopyrimdin-4-one representation. Therefore, all embodiments are presented as pyrazolopyrimdin-4-one-derivatives or more precisely as pyrazolo[3,4-d]pyrimidin-4-one derivatives.

"**Bonds**": If within a chemical formula of a ring system or a defined group a substituent is directly linked to an atom or a group like "RyR" in below formula this shall mean that the substituent is only attached to the corresponding atom. If however from another substituent like "RxR" a bond is not specifically linked to an atom of the ring system but drawn towards the centre of the ring or group this means that this substituent "RxR" may be linked to any meaningful atom of the ring system / group unless stated otherwise.



The bond symbol "-" (= minus sign) or the symbol "- *" (= minus sign followed by an asterisk sign) stands for the bond through which a substituent is bound to the corresponding remaining part of the molecule / scaffold. In cases in that minus sign does not seem to be sufficiently clear, an asterisk is added to the bond symbol "-" in order to determine the point of attachment of said bond with the corresponding main part of the molecule / scaffold.

In general, the bond to one of the herein defined heterocycloalkyl, heterocyclyl or heteroaryl groups may be effected via a C atom or optionally an N atom.

The term "**aryl**" used in this application denotes a phenyl, biphenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl group, preferably it denotes a phenyl or

naphtyl group, more preferably a phenyl group. This definition applies for the use of "**aryl**" in any context within the present description in the absence of a further definition.

The term "**C_{1-n}-alkyl**" denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms, wherein n is a figure selected from the group of 2, 3, 4, 5, 6, 7, 8, 9, or 10, preferably from the group of 2, 3, 4, 5, or 6, more preferably from the group of 2, 3, or 4. Examples of such groups include methyl, ethyl, *n*-propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *tert*-pentyl, *n*-hexyl, *iso*-hexyl etc. As will be evident from the context, such **C_{1-n}-alkyl** group optionally can be substituted.

This definition applies for the use of "**alkyl**" in any reasonable context within the present description in the absence of a further definition.

In cases in which the term "**C_{1-n}-alkyl**" is used in the middle of two other groups / substituents, like for example in "**C_{1-n}-cylcoalkyl-C_{1-n}-alkyl-O-**", this means that the "C_{1-n}-alkyl"-moiety bridges said two other groups. In the present example it bridges the C_{1-n}-cylcoalkyl with the oxygen like in "cyclopropyl-methyl-oxy-". It will be evident, that in such cases "C_{1-n}-alkyl" has the meaning of a "C_{1-n}-alkylene" spacer like methylene, ethylene etc. The groups that are bridged by "C_{1-n}-alkyl" may be bound to "C_{1-n}-alkyl" at any position thereof. Preferably the right hand group is located at the distal right hand end of the alkyl group and left hand group at the distal left hand side of the alkyl group. The same applies for other substituents.

The term "**C_{2-n}-alkenyl**" denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and at least one C=C group (i.e. carbon – carbon double bond), wherein n preferably has a value selected from the group of 3, 4, 5, 6, 7, or 8, more preferably 3, 4, 5, or 6, more preferably 3 or 4. Examples of such groups include ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl etc. As will be evident from the context, such **C_{2-n}-alkenyl** group optionally can be substituted.

This definition applies for the use of "**alkenyl**" in any reasonable context within the present description in the absence of a further definition if no other definition.

In cases in which the term "**C_{2-n}-alkenyl**" is used in the middle of two other groups / substituents, the analogue definition as for C_{1-n}-alkyl applies.

The term "**C_{2-n}-alkynyl**" denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and at least one C≡C group (i.e. a carbon-carbon triple bond), wherein n preferably has a value selected from the group of 3, 4, 5, 6, 7, or 8, more preferably 3, 4, 5, or 6, more preferably 3 or 4. Examples of such groups include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl etc. As will be evident from the context, such **C_{2-n}-alkynyl** group optionally can be substituted.

This definition applies for the use "**alkynyl**" in any reasonable context within the present description in the absence of a further definition.

In cases in which the term "**C_{2-n}-alkynyl**" is used in the middle of two other groups / substituents, the analogue definition as for C_{1-n}-alkyl applies.

The term "**C_{3-n}-cycloalkyl**" denotes a saturated monocyclic group with 3 to n C ring atoms. n preferably has a value of 4 to 8 (= 4, 5, 6, 7, or 8), more preferably 4 to 7, more preferably such C_{3-n}-cycloalkyl is 5 or 6 membered. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl etc.. This definition applies for "**cycloalkyl**" in any reasonable context within the present description in the absence of a further definition.

The term "**halogen**" denotes an atom selected from among F, Cl, Br, and I.

The term "**heteroaryl**" used in this application denotes a heterocyclic, mono- or bicyclic aromatic ring system which includes within the ring system itself in addition to at least one C atom one or more heteroatom(s) independently selected from N, O, and/or S. A monocyclic ring system preferably consists of 5 to 6 ring members, a bicyclic ring system preferably consists of 8 to 10 ring members. Preferred are

heteroaryls with up to 3 heteroatoms, more preferred up to 2 heteroatoms, more preferred with 1 heteroatom. Preferred heteroatom is N. Examples of such moieties are benzimidazolyl, benzisoxazolyl, benzo[1,4]-oxazinyl, benzoxazol-2-onyl, benzofuranyl, benzoisothiazolyl, 1,3-benzodioxolyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzoxadiazolyl, benzoxazolyl, chromanyl, chromenyl, chromonyl, cinnolinyl, 2,3-dihydrobenzo[1,4]dioxinyl, 2,3-dihydrobenzofuranyl, 3,4-dihydrobenzo[1,4]oxazinyl, 2,3-dihydroindolyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydroisoindolyl, 6,7-dihydropyrrolizinyl, dihydroquinolin-2-onyl, dihydroquinolin-4-onyl, furanyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*a*]pyridyl, imidazolyl, imidazopyridyl, imidazo[4,5-d]thiazolyl, indazolyl, indolizinyl, indolyl, isobenzofuranyl, isobenzothienyl, isochromanyl, isochromenyl, isoindoyl, isoquinolin-2-onyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, 1,2,4-oxadiazoyl, 1,3,4-oxadiazoyl, 1,2,5-oxadiazoyl, oxazolopyridyl, oxazolyl, 2-oxo-2,3-dihydrobenzimidazolyl, 2-oxo-2,3-dihydroindolyl, 1-oxoindanyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidinyl, pyrazolyl, pyridazinyl, pyridopyrimidinyl, pyridyl (pyridinyl), pyridyl-*N*-oxide, pyrimidinyl, pyrimidopyrimidinyl, pyrrolopyridyl, pyrrolopyrimidinyl, pyrrolyl, quinazolinyl, quinolin-4-onyl, quinolinyl, quinoxalinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, tetrazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, thiazolyl, thieno[2,3-*d*]imidazolyl, thieno[3,2-*b*]pyrrolyl, thieno[3,2-*b*]thiophenyl, thienyl, triazinyl, or triazolyl.

Preferred heteroaryl groups are furanyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, thienyl, and thiazolyl.

More preferred heteroaryl groups are oxadiazolyl, triazolyl, pyrazolyl, furanyl, and pyridyl, more preferred is pyrazolyl and pyridyl.

The definition pyrazole includes the isomers 1H-, 3H- and 4H-pyrazole. Preferably pyrazolyl denotes 1H-pyrazolyl.

The definition imidazole includes the isomers 1H-, 2H- and 4H-imidazole. A preferred definition of imidazolyl is 1H-imidazolyl.

The definition triazole includes the isomers 1H-, 3H- and 4H-[1,2,4]-triazole as well as 1H-, 2H- and 4H-[1,2,3]-triazole. The definition triazolyl therefore includes 1H-[1,2,4]-triazol-1-, -3- and -5-yl, 3H-[1,2,4]-triazol-3- and -5-yl, 4H-[1,2,4]-triazol-3-, -4- and -5-yl, 1H-[1,2,3]-triazol-1-, -4- and -5-yl, 2H-[1,2,3]-triazol-2-, -4- and -5-yl as well as 4H-[1,2,3]-triazol-4- and -5-yl.

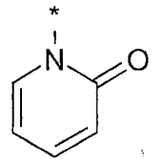
The term tetrazole includes the isomers 1H-, 2H- and 5H-tetrazole. The definition tetrazolyl therefore includes 1H-tetrazol-1- and -5-yl, 2H-tetrazol-2- and -5-yl and 5H-tetrazol-5-yl.

The definition indole includes the isomers 1H- and 3H-indole. The term indolyl preferably denotes 1H-indol-1-yl.

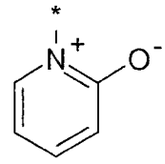
The term isoindole includes the isomers 1H- and 2H-isoindole.

This definition applies for "**heteroaryl**" in any reasonable context within the present description in the absence of a further definition.

The term "**N-linked-pyridine-2-one**" used in this application denotes:



and its tautomeric form



The term "**heterocycloalkyl**" within the context of the present invention denotes a saturated 3 to 8 membered, preferably 5-, 6- or 7-membered ring system or a 5-12 membered bicyclic ring system, which include 1, 2, 3 or 4 heteroatoms, selected from N, O, and/or S. Preferred are 1, 2, or 3 heteroatoms.
The preferred number of carbon atoms is 3 to 7 with 1, 2, 3 or 4 heteroatoms selected from N, O, and/or S. Such heterocycloalkyl groups are addressed as C_{3-7}-heterocycloalkyl.
Preferred are saturated heterocycloalkyl rings with 5, 6, or 7 ring atoms, of which 1 or 2 are heteroatoms and the remaining are C-atoms.

Wherever C_{3-7}-heterocycloalkyl- substituents are mentioned, the preferred embodiments thereof are 5-, 6-,- or 7-membered cycles, more preferably monocycles. They include 1, 2, 3, or 4 heteroatoms, selected from N, O, and/or S, whereby 1 or 2 such heteroatoms are preferred, more preferably 1 such heteroatom.

Preferred example for heterocycloalkyl include morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, oxathianyl, dithianyl, dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dioxolanyl, oxathiolanyl, imidazolidinyl, tetrahydropyranyl, pyrrolinyl, tetrahydrothienyl, oxazolidinyl, homopiperazinyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, azetidinyl, 1,3-diazacyclohexanyl or pyrazolidinyl group.

This definition applies for "**heterocycloalkyl**" in any reasonable context within the present description in the absence of a further specific definition.

The term "**heterocyclyl**" specifically is used to define the group ***Hc*** in formula I and formulae which are derived thereof and therefore will be independently used from the definition of "heterocycloalkyl". However, the definitions for "heterocycloalkyl" shall be comprised within the definition for "heterocyclyl". ***Hc*** is a group which is or at least comprises a non-aromatic heterocycloalkyl group which is bound to the scaffold.

Within the context of the present invention and as used herein, specifically within the context of ***Hc***, "**heterocyclyl**" means a non-aromatic monocyclic, bicyclic or tricyclic ring system, whereby the ring members are carbon atoms and at least one, preferably one to three heteroatom(s) selected from the group of nitrogen, oxygen, or sulphur, the sulphur being part the group $-S(O)_r$ - with r being 0, 1 or 2. Such ring system may further be bridged. Such systems also will be called heteromonocyclic, heterobicyclic, or heterotricyclic ring system within the present context.

This heterocyclyl group may be saturated or partly unsaturated, whereby in systems with more than one ring system, at least one of them is not aromatic. This at least one non aromatic ring system comprises said at least one heteroatom.

This heterocyclyl group may be bound to the scaffold in more than one way. If no particular bonding arrangement is specified, then all possible arrangements are

intended. For example, the term "tetrahydropyranyl" includes 2-, 3-, or 4-tetrahydropyranyl and the like. In cases with more than one ring system, the bonding to the scaffold is via at least one ring atom of the non aromatic ring system comprising at least one heteroatom. Preferably this heterocyclyl-group is bound to the scaffold via a nitrogen atom or one of the saturated carbon atoms in said ring system. More preferably it is attached to the scaffold via a carbon atom of the non-aromatic heterocyclic ring system.

Such heterocyclyl group may be fused, respectively annelated, with a cycloalkyl, another heterocyclic group, an aromatic ring system, such as phenyl or may be part of a spirocyclic system. In a fused or annelated system, the two ring systems share a bond between two adjacent ring atoms. In the spiro variation, the two ring systems have one ring atom in common.

The monoheterocyclic ring systems within this definition are non-aromatic monocyclic ring systems, in which at least one, preferably one to three, of the carbon atoms have been replaced with a heteroatom such as nitrogen, oxygen, or sulphur, the sulphur being part the group – $S(O)_r$ - with r being 0, 1 or 2 comprises preferably 4 to 8 ring atoms. Within this context preferred are 5-, 6- or 7-membered, saturated or at least partly unsaturated heterocyclic rings

The heterobicyclic ring systems within this definition are bicyclic ring systems with at least one, preferably one to three, of the carbon atoms have been replaced with a heteroatom such as nitrogen, oxygen, or sulphur, the sulphur being part the group – $S(O)_r$ - with r being 0, 1 or 2; the ring system has at least one non-aromatic ring, which comprises said at least one heteroatom, and the bicyclic ring system comprises preferably 7 to 12 ring atoms. Within this context preferred are 8-, 9- or 10-membered, saturated or at least partly unsaturated heterocyclic rings.

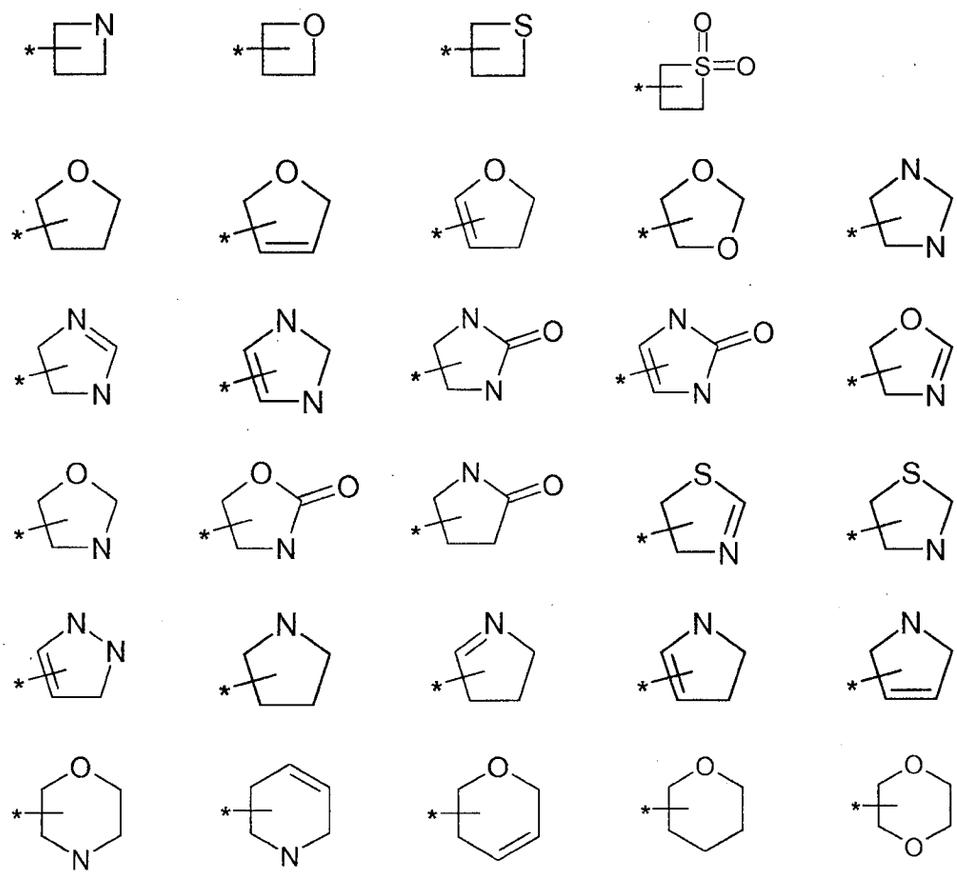
The heterotricyclic ring systems within this definition are tricyclic systems of annelated monocycles, in which at least one, preferably one to three, of the carbon atoms have been replaced with a heteroatom such as nitrogen, oxygen, or sulphur, the sulphur being part the group – $S(O)_r$ - with r being 0, 1 or 2; the ring system has

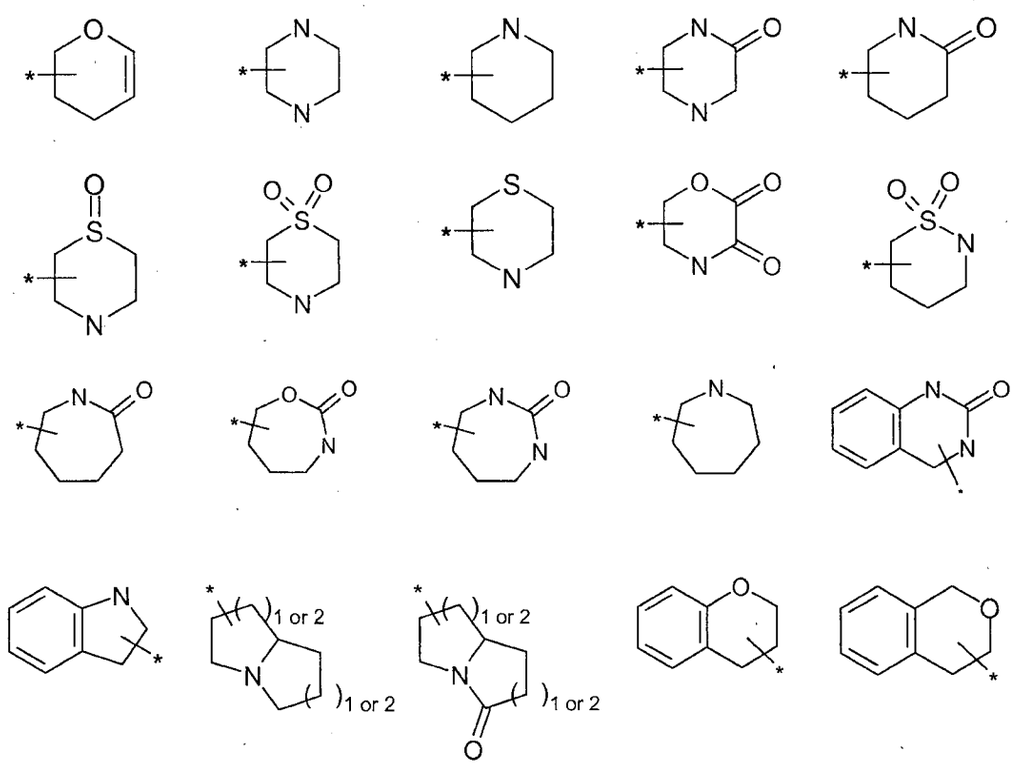
at least one non-aromatic ring, which comprises said at least one heteroatom, and the tricyclic ring system comprises preferably 7 to 14 ring atoms.

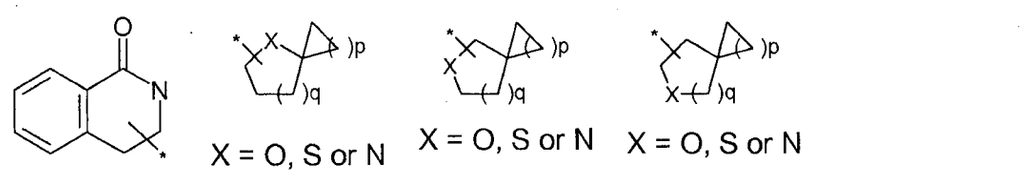
By the term spirocyclic system as mentioned within this definition, are meant preferably 5-10 membered, spirocyclic rings which may optionally contain 1, 2 or 3 heteroatoms, selected from among oxygen, sulphur, and nitrogen. Such systems optionally may be annelated with an aromatic ring system such as phenyl.

The order of preference of heterocyclic ring systems is: monocyclic ring systems are more preferred than bicyclic ring systems, which are more preferred than tricyclic ones.

Examples for such heterocyclic ***Hc*** groups according to the present invention are the following groups:







X = O, S or N
p = 1, 2, 3, 4 or 5
q = 1, 2 or 3

X = O, S or N
p = 1, 2, 3, 4 or 5
q = 1, 2 or 3

X = O, S or N
p = 1, 2, 3, 4 or 5
q = 1, 2 or 3

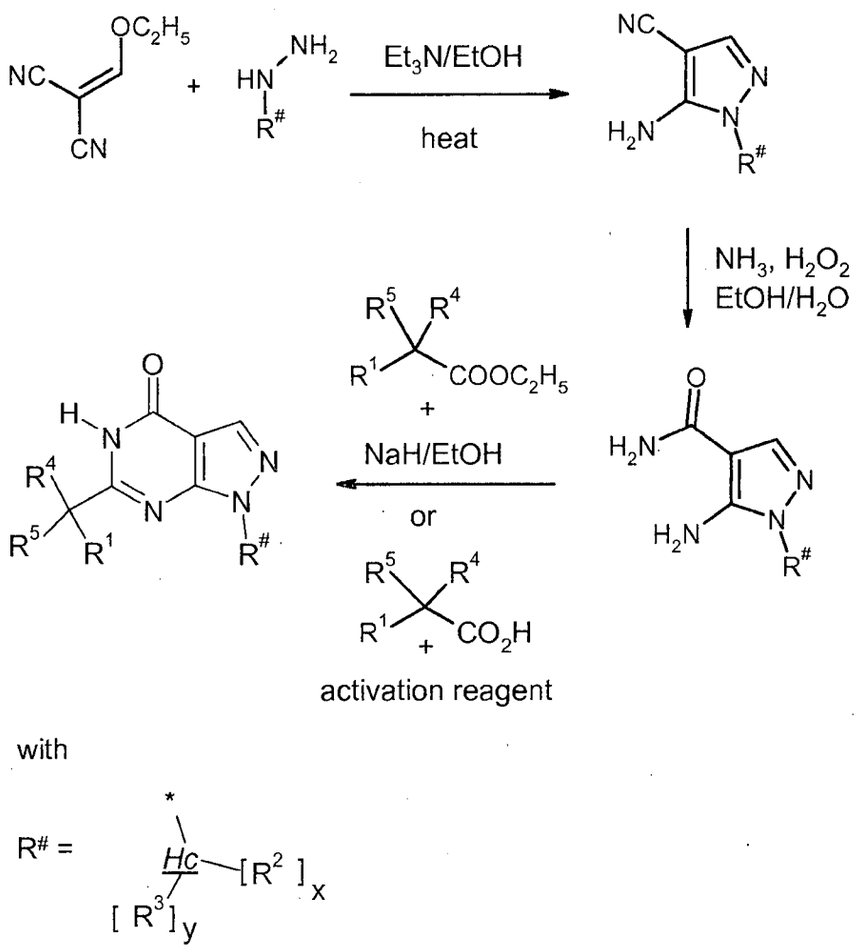
, wherein -* stands for the bond by which said group is bound to the nitrogen atom of the scaffold, that is numbered as 1.

The above definition applies for "**heterocyclyl**" in any reasonable context within the present description in the absence of a further definition.

The term "**oxo**" denotes an oxygen atom as substituent that is bonded by a double bond, preferably it is bonded to a C-atom. In case oxo is used as a substituent, the oxo replaces two hydrogen atoms of the corresponding atom of the unsubstituted compound.

The following schemes shall illustrate a process to manufacture the compounds of the present invention by way of example:

Scheme 1

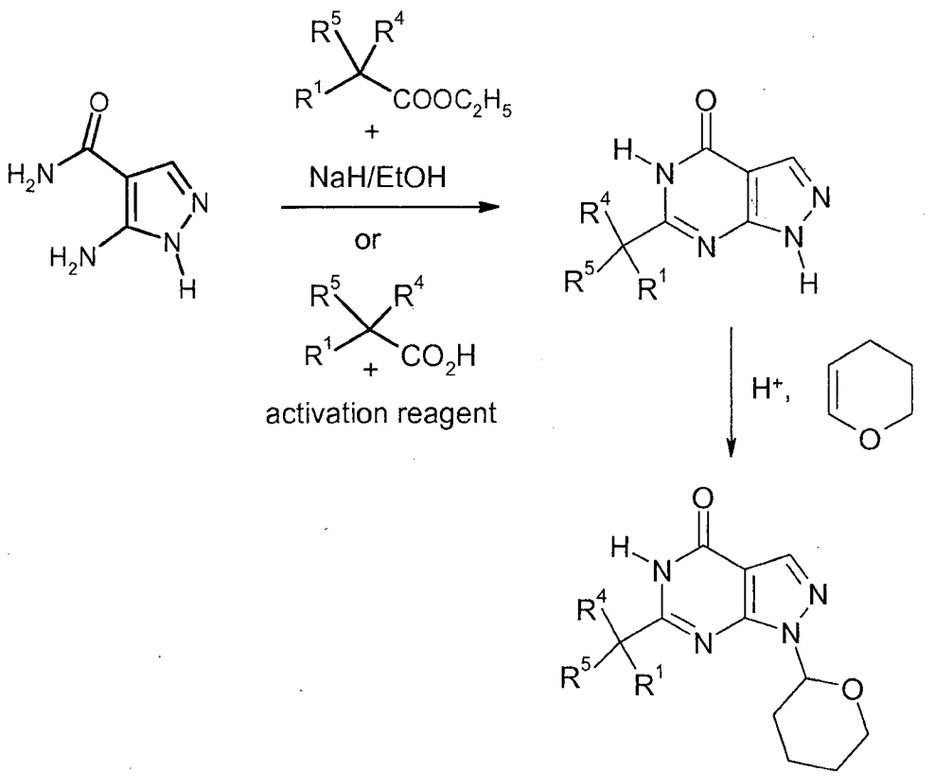


Scheme 1: In a first step 2-ethoxymethylene-malononitrile is condensed with mono-substituted hydrazines by heating in an appropriate solvent like ethanol in the presence of a base (e.g. triethylamine) to form 5-amino-1H-pyrazole-4-carbonitriles.

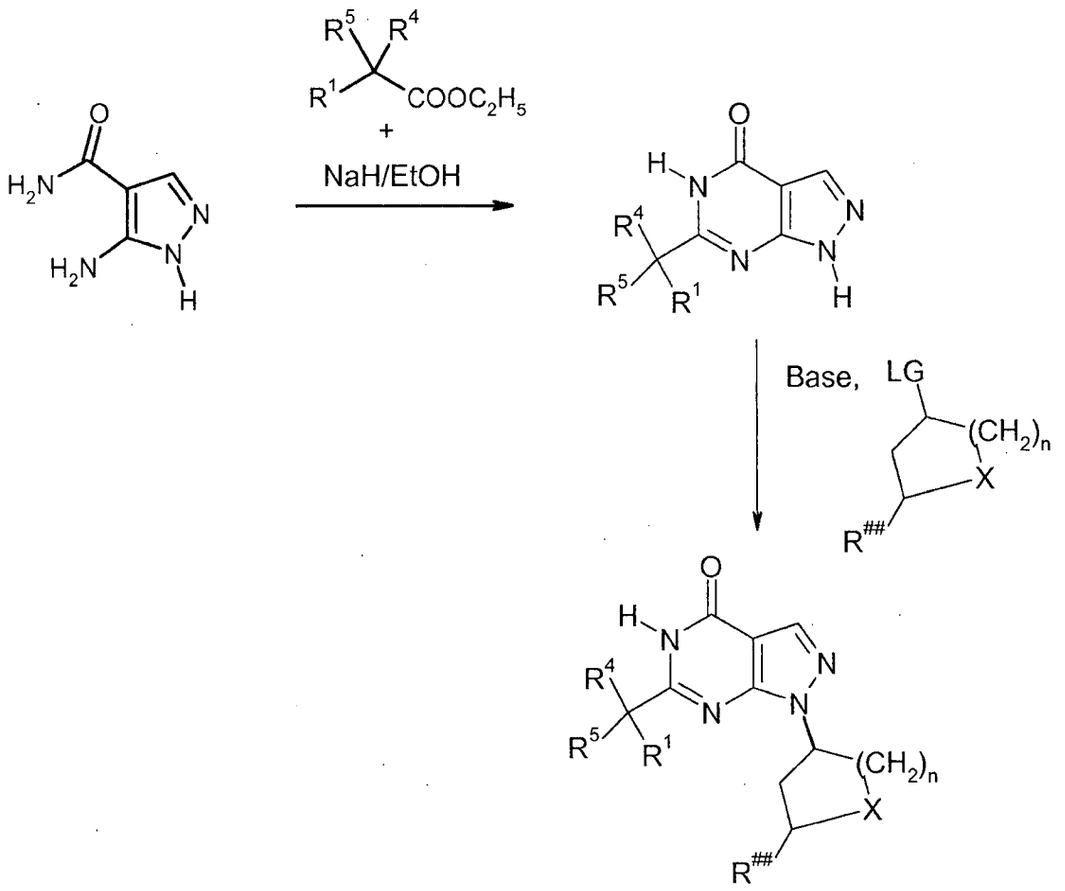
These compounds are converted in a second step to the corresponding amides, e.g. by treatment of an ethanolic solution with ammonia (25 % in water) and hydrogen peroxide (35 % in water). In a third step, heating with carboxylic esters under basic conditions (e.g sodium hydride in ethanol) or carboxylic acids with an activation reagent (e.g. polyphosporic acid) leads to pyrazolo[3,4-d]pyrimidin-4-ones as final products [cf., for example, A. Miyashita *et al.*, *Heterocycles* **1990**, *31*, 1309ff].

Schemes 2 and 3 illustrate alternative methods to prepare the final compounds: in these exemplified manufacturing methods 5-amino-1H-pyrazole-4-carboxylic acid amides are condensed in a first step with an appropriate ester derivative followed in a second step by alkylation with suitable electrophiles.

Scheme 2



Scheme 3



X = O, NH, NR^2, S, SO or SO_2

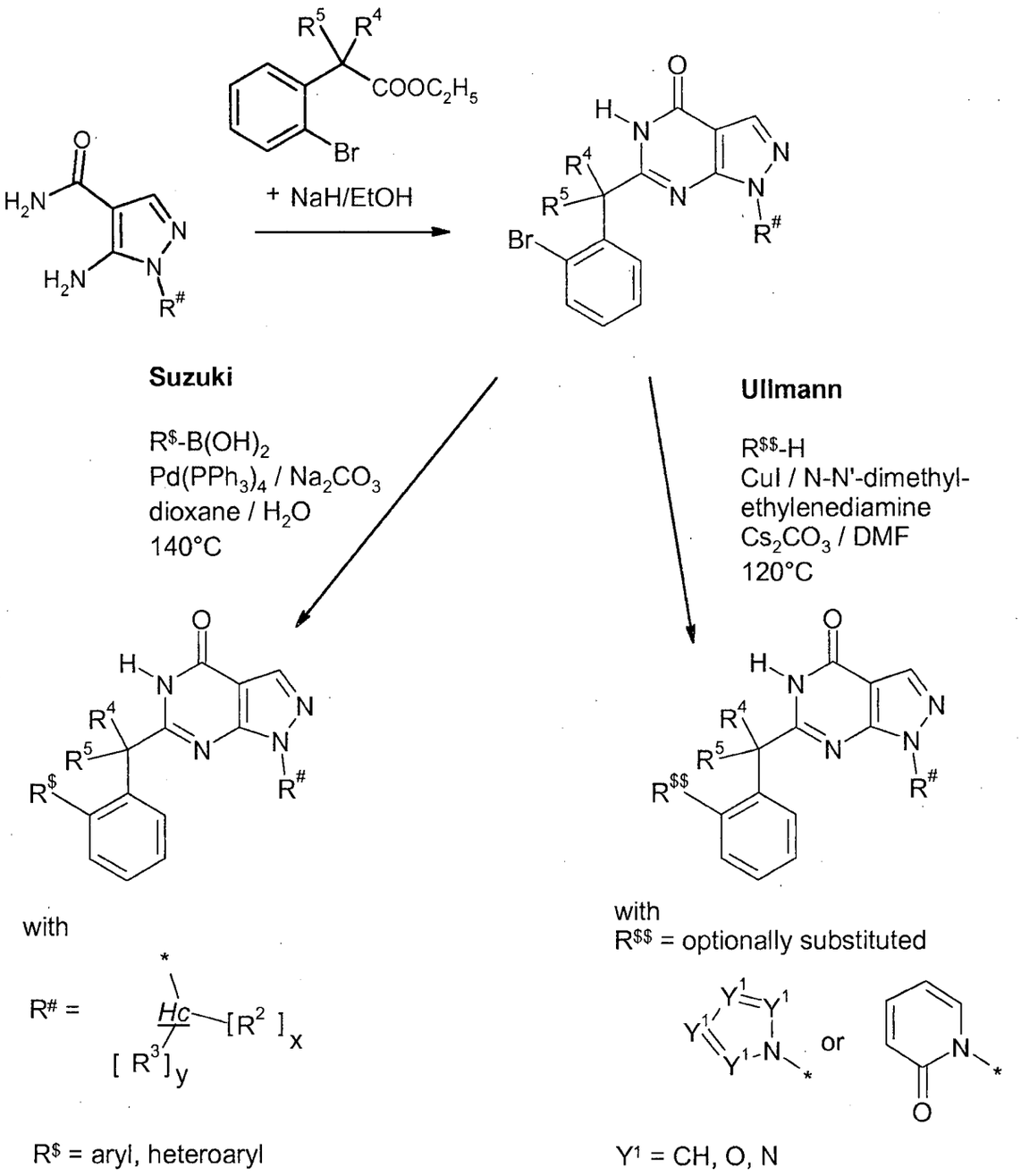
$R^{\#\#}$ = R^2 or R^3

LG = Br-, Cl-, I-, CH_3-SO_2-O-, p-toluenesulphonyl-

n = 1,2

Scheme 4 illustrates alternative methods to prepare the final compounds: in the exemplified manufacturing methods 5-amino-1H-pyrazole-4-carboxylic acid amides are condensed in a first step with (2-bromo-phenyl)-acetic acid ester derivatives followed in a second step by substitution of the bromine atom by an aromatic or heteroaromatic residue e.g. using Suzuki or Ullmann type reaction conditions.

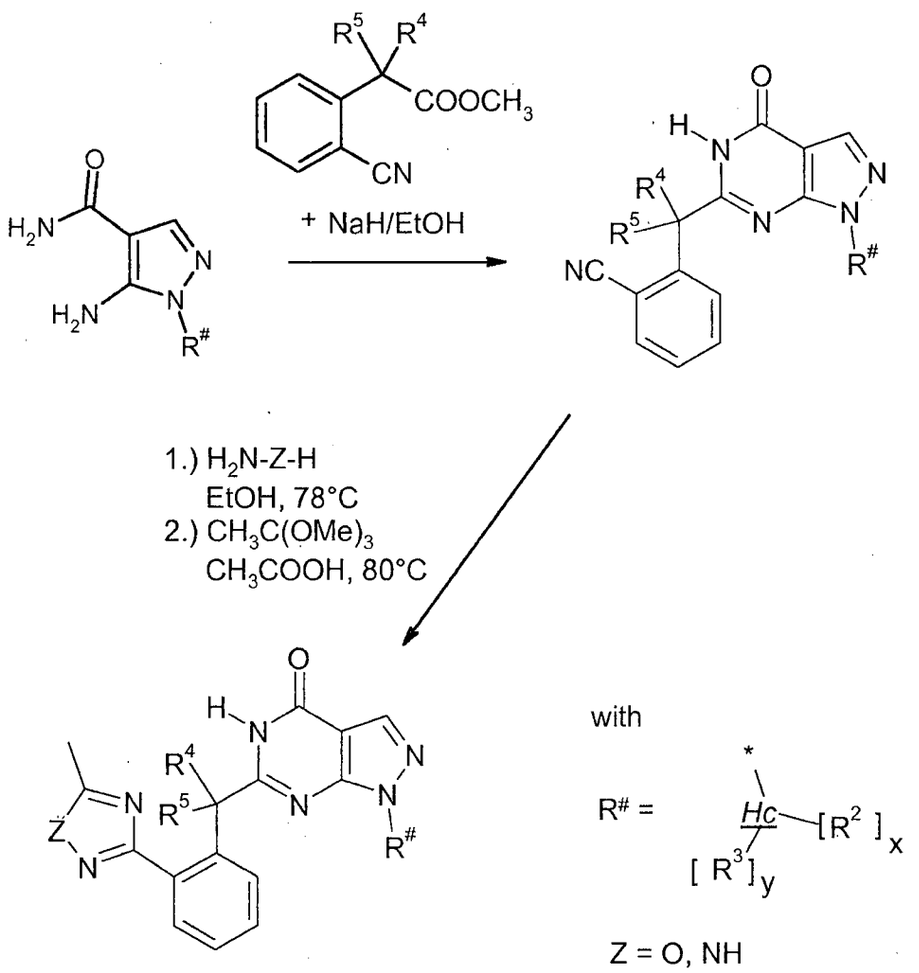
Scheme 4



Scheme 5 illustrates an alternative method to prepare the final compounds: in the exemplified manufacturing method 5-amino-1H-pyrazole-4-carboxylic acid amides are condensed in a first step with (2-cyano-phenyl)-acetic acid ester derivatives followed in

a second step by transformation of the nitrile group into a 5-membered heteroaromatic group.

Scheme 5

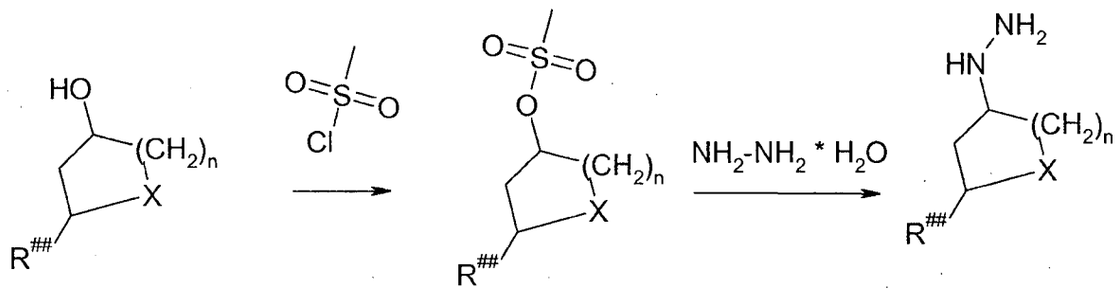


Further alternative processes for preparing pyrazolo[3,4-d]pyrimidin-4-ones are known in the art and can likewise be employed for synthesizing the compounds of the invention (see, for example: P. Schmidt *et al.*, *Helvetica Chimica Acta* **1962**, *189*, 1620ff.).

The mono-substituted hydrazine derivatives, that are used in step 1 of scheme 1 can be prepared either by nucleophilic displacement on the corresponding mesylate derivative (scheme 6) or by reduction of the hydrazone intermediate as depicted in scheme 7 [cf.,

for example, J.W. Timberlake *et al.*, "*Chemistry of Hydrazo-,Azo-, and Azoxy Groups*"; *Patai,S.,Ed.;* 1975, *Chapter 4*; S. C. Hung *et al.*, *Journal of organic Chemistry 1981*, 46, 5413-5414].

Scheme 6

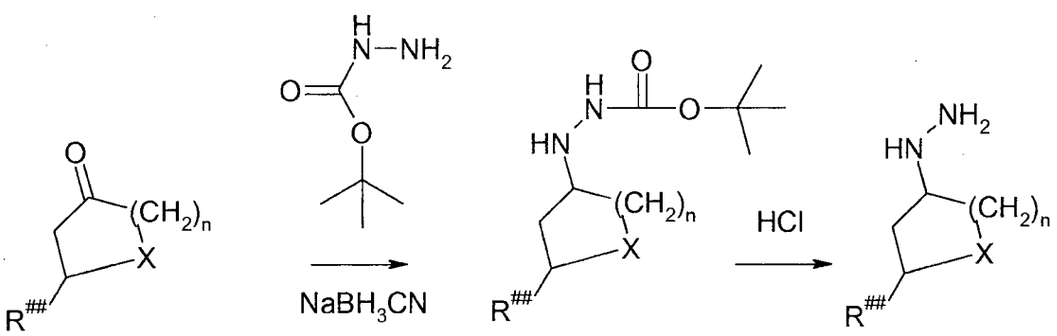


X = O, NH, NR^2, S, SO or SO_2

$R^{##}$ = R^2 or R^3

n = 1,2

Scheme 7



X = O, NH, NR^2, S, SO or SO_2

$R^{##}$ = R^2 or R^3

n = 1,2

Further information also can be found in WO04099210 (in particular page 9, last paragraph to page 14, line 8, incorporated by reference).

The compounds of the invention show a valuable range of pharmacological effects which could not have been predicted. They are characterised in particular by inhibition of PDE9A.

Preferably the compounds according to the present invention show a high selectivity profile in view of inhibiting or modulating specific members within the PDE9 family or other PDE families, with a clear preference (selectivity) towards PDE9A inhibition.

The compounds of the present invention are supposed to show a favourable safety profile.

METHOD OF TREAMENT

The present invention refers to compounds, which are considered effective and selective inhibitors of phosphodiesterase 9A and can be used for the development of medicaments. Such medicaments shall preferably be used for the treatment of diseases in which the inhibition of PDE9A can evolve a therapeutic, prophylactic or disease modifying effect. Preferably the medicaments shall be used to improve perception, concentration, cognition, learning or memory, like those occurring in particular in situations/diseases/syndromes such as mild cognitive impairment, age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

Another aspect of the present invention concerns the treatment of a disease which is accessible by PDE9A modulation, in particular sleep disorders like insomnia or narcolepsy, bipolar disorder, metabolic syndrome, obesity, diabetis mellitus, including

type 1 or type 2 diabetes, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

Thus the medical aspect of the present invention can be summarised in that it is considered that a compound according to any of the genius embodiments of the invention as outlined herein, in particular the one according to formula I as defined by each of the aspects 1 – 17, each of the elements/embodiments of matrix 0 or matrix I or a compound selected from the group of the exemplified final compounds (see aspect 18 or chapter exemplary embodiments) is used as a medicament.

Such a medicament preferably is for the treatment of a CNS disease.

In an alternative use, the medicament is for the treatment of a CNS disease, the treatment of which is accessible by the inhibition of PDE9.

In an alternative use, the medicament is for the treatment of a disease that is accessible by the inhibition of PDE9.

In an alternative use, the medicament is for the treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

In an alternative use, the medicament is for the treatment amelioration and / or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

In an alternative use, the medicament is for the treatment of Alzheimer's disease.

In an alternative use, the medicament is for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetis mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

PHARMACEUTICAL COMPOSITIONS

Medicaments for administration comprise a compound according to the present invention in a therapeutically effective amount. By "therapeutically effective amount" it is meant that if the medicament is applied via the appropriate regimen adapted to the patient's condition, the amount of said compound of formula (I) will be sufficient to effectively treat, to prevent or to decelerate the progression of the corresponding disease, or otherwise to ameliorate the estate of a patient suffering from such a disease. It may be the case that the "therapeutically effective amount" in a mono-therapy will differ from the "therapeutically effective amount" in a combination therapy with another medicament.

The dose range of the compounds of general formula (I) applicable per day is usually from 0.1 to 5000 mg, preferably 0.1 to 1000 mg, preferably from 2 to 500 mg, more preferably from 5 to 250 mg, most preferably from 10 to 100 mg. A dosage unit (e.g. a tablet) preferably contains between 2 and 250 mg, particularly preferably between 10 and 100 mg of the compounds according to the invention.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age, weight, gender or other condition of the patient, route of administration, severity of disease, and the like.

The compounds according to the invention may be administered by oral, parenteral (intravenous, intramuscular etc.), intranasal, sublingual, inhalative, intrathecal, topical or rectal route. Suitable preparations for administering the compounds according to the present invention include for example patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions,

suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.- %, preferably 0.1 to 50 wt.- % of the composition as a whole. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

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

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

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

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

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

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

For oral use the tablets may obviously contain, in addition to the carriers specified, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additional substances such as starch, preferably potato starch, gelatin and the like. Lubricants such as magnesium stearate, sodium laurylsulphate and talc may also be used to produce the tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients.

The dosage of the compounds according to the invention is naturally highly dependent on the method of administration and the complaint which is being treated. When administered by inhalation the compounds of formula (I) are characterised by a high potency even at doses in the microgram range. The compounds of formula (I) may also be used effectively above the microgram range. The dosage may then be in the gram range, for example.

COMBINATIONS WITH OTHER ACTIVE SUBSTANCES

In another aspect the present invention relates to the above-mentioned pharmaceutical formulations as such which are characterised in that they contain a compound according to the present invention.

A further aspect of the present invention refers to a combination of each of the compounds of the present invention, preferably at least one compound according to the present invention with another compound selected from the group of for example beta-secretase inhibitors; gamma-secretase inhibitors; gamma-secretase modulators; amyloid aggregation inhibitors such as e.g. alzhemed; directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants, such as e.g. vitamin E , ginko biloba or ginkolide; anti-inflammatory substances, such as e.g. Cox inhibitors, NSAIDs additionally or exclusively having Aß lowering properties; HMG-CoA reductase inhibitors, such as statins; acetylcholine esterase inhibitors, such as donepezil, rivastigmine, tacrine, galantamine; NMDA receptor antagonists such as e.g. memantine; AMPA receptor agonists; AMPA receptor positive modulators, AMPkines - monoamine receptor reuptake inhibitors; substances modulating the concentration or release of neurotransmitters; substances inducing the secretion of growth hormone such as ibutamoren mesylate and capromorelin; CB-1 receptor antagonists or inverse agonists; antibiotics such as minocyclin or rifampicin; PDE1, PDE2, PDE4, PDE5 and / or PDE10 inhibitors, GABAA receptor inverse agonists; GABAA receptor antagonists; nicotinic receptor agonists or partial agonists; alpha4beta2 nicotinic receptor agonists or partial agonists; alpha7 nicotinic receptor agonists or partial agonists; histamine receptor H3 antagonists; 5-HT4 receptor agonists or partial agonists; 5-HT6 receptor antagonists; alpha2-adrenoreceptor antagonists, calcium antagonists; muscarinic receptor M1 agonists or positive modulators; muscarinic receptor M2 antagonists; muscarinic receptor M4 antagonists; metabotropic glutamate receptor 5 positive modulators; metabotropic glutamate receptor 2 antagonists, and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced.

This invention further relates to pharmaceutical compositions containing one or more, preferably one active substance, which is selected from the compounds according to

the invention and/or the corresponding salts, as well as one or more, preferably one active substance selected from among alzhemed, vitamin E, ginkolide, donepezil, rivastigmine, tacrine, galantamine, memantine, ibutamoren mesylate, capromorelin, minocyclin and/or rifampicin, optionally together with one or more inert carriers and/or diluents.

The compounds according to the invention may also be used in combination with immunotherapies such as e.g. active immunisation with Abeta or parts thereof or passive immunisation with humanised anti-Abeta antibodies or antibodyfragments or nanobodies for the treatment of the above-mentioned diseases and conditions.

The combinations according to the present invention may be provided simultaneously in one and the same dosage form, i.e. in form of a combination preparation, for example the two components may be incorporated in one tablet, e. g. in different layers of said tablet. The combination may be also provided separately, in form of a free combination, i.e the compounds of the present invention are provided in one dosage form and one or more of the above mentioned combination partners is provided in another dosage form. These two dosage forms may be equal dosage forms, for example a co-administration of two tablets, one containing a therapeutically effective amount of the compound of the present invention and one containing a therapeutically effective amount of the above mentioned combination partner. It is also possible to combine different administration forms, if desired. Any type of suitable administration forms may be provided.

The compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may be used simultaneously or at staggered times, but particularly close together in time. If administered simultaneously, the two active substances are given to the patient together; if administered at staggered times the two active substances are given to the patient successively within a period of less than or equal to 12, particularly less than or equal to 6 hours.

The dosage or administration forms are not limited, in the frame of the present invention any suitable dosage form may be used. Exemplarily the dosage forms may

be selected from solid preparations such as patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions, suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like.

The dosage forms are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of each active component being present. Depending from the administration route and dosage form the ingredients are selected accordingly.

The dosage for the above-mentioned combination partners is expediently 1/5 of the normally recommended lowest dose up to 1/1 of the normally recommended dose.

The dosage forms are administered to the patient for example 1, 2, 3, or 4 times daily depending on the nature of the formulation. In case of retarding or extended release formulations or other pharmaceutical formulations, the same may be applied differently (e.g. once weekly or monthly etc.). It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily.

EXAMPLES

PHARMACEUTICAL COMPOSITIONS

The following pharmaceutical formulations may illustrate the present invention without restricting its scope:

Some examples of formulations will now be described, wherein the term "active substance" denotes one or more compounds according to the invention including the salts thereof. In the case of one of the aforementioned combinations with one or more other active substances the term "active substance" also includes the additional active substances.

Example A

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

Example B

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Diameter: 10 mm, flat

Example C

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance	150.0 mg
corn starch (dried)	approx. 80.0 mg
lactose (powdered)	approx. 87.0 mg
magnesium stearate	3.0 mg
	approx. 320.0 mg

Capsule shell: size 1 hard gelatine capsule.

Example D

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Example E

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid	q.s.	
double-distilled water	ad	2.0 mL

Example F

Ampoules containing 50 mg of active substance

Composition:

active substance		50.0 mg
0.01 N hydrochloric acid	q.s.	
double-distilled water	ad	10.0 mL

The preparation of any the above mentioned formulations can be done following standard procedures.

BIOLOGICAL ASSAY

The in vitro effect of the compounds of the invention can be shown with the following biological assays.

PDE9A2 assay protocol:

The PDE9A2 enzymatic activity assay was run as scintillation proximity assay (SPA), in general according to the protocol of the manufacturer (Amersham Biosciences, product number: TRKQ 7100).

As enzyme source, lysate (PBS with 1 % Triton X-100 supplemented with protease inhibitors, cell debris removed by centrifugation at 13.000 rpm for 30 min) of SF 9 cell expressing the human PDE9A2 was used. The total protein amount included in the assay varied upon infection and production efficacy of the SF9 cells and lay in the range of 0.1 – 100 ng.

In general, the assay conditions were as follows:

- total assay volume: 40 microliter
- protein amount: 0.1 – 50 ng
- substrate concentration (cGMP): 20 naomolar; ~1 mCi/l
- incubation time: 60 min at room temperature
- final DMSO concentration: 0.2 - 1 %

The assays were run in 384-well format. The test reagents as well as the enzyme and the substrate were diluted in assay buffer. The assay buffer contained 50 mM

Tris, 8.3 mM MgCl2, 1.7 mM EGTA, 0.1 % BSA, 0.05 % Tween 20; the pH of assay buffer was adjusted to 7.5. The reaction was stopped by applying a PDE9 specific inhibitor (e.g. compounds according to WO04099210) in excess.

Determination of % inhibition:

The activity of the positive control (minus the negative control = background) is set to 100 % and activity in the presence of test compound is expressed relative to these 100 %. Within this setting, an inhibition above 100 % might be possible due to the nature of the variation of the positive control within the assay, however, in this case the reported % inhibition had been adjusted to 100 %.

Determination of IC_{50}:

IC_{50} can be calculated with GraphPadPrism or other suited software setting the positive control as 100 and the negative control as 0. For calculation of IC_{50} dilutions of the test compounds (substrates) are to be selected and tested following the aforementioned protocol.

Data

In the following, % inhibition data will illustrate that the compounds according to the present invention are suited to inhibit PDE9 and thus provide useful pharmacological properties. The examples are not meant to be limiting. The table also provides IC_{50} values. The values are presented as being within a nanomolar range (nM), i.e. within the range of either 1 nanomolar to 100 nanomolar or within the range of 101 nanomolar to 1200 nanomolar. The specific IC_{50} value is within said range. The example number refer to the final examples as outlined in the section **Exemplary embodiments** (see also aspect 18 of the invention).

All data are measured according to the procedure described herein.

Example No.	% inhibition of PDE9A2 (at 10 micromolar concentration)	IC_{50} within range [nanomolar (nM)]
1	100	1 - 100
2	99	1 - 100
3	99	1 - 100
4	98	1 - 100
5	99	1 - 100
6	98	1 - 100
7	98	1 - 100
8	100	1 - 100
9	99	1 - 100
10	98	1 - 100
11	98	1 - 100
12	97	1 - 100
13	90	101 - 1200
14	96	101 - 1200
15	92	101 - 1200
16	86	101 - 1200
17	100	1 - 100
18	99	1 - 100
19	99	1 - 100
20	98	1 - 100
21	97	101 - 1200
22	98	1 - 100
23	99	1 - 100
24	86	101 - 1200
25	96	1 - 100
26	91	101 - 1200
27	99	1 - 100
28	98	1 - 100

Example No.	% inhibition of PDE9A2 (at 10 micromolar concentration)	IC_{50} within range [nanomolar (nM)]
29	96	1 - 100
30	100	1 - 100
31	98	1 - 100
32	100	1 - 100
33	97	1 - 100
34	93	101 - 1200
35	100	101 - 1200
36	100	1 - 100
37	97	1 - 100
38	99	1 - 100
39	99	1 - 100
40	99	1 - 100
40-1	100	1 - 100
40-2	100	1 - 100
40-3	100	101 - 1200
40-4	92	101 - 1200
40-5	98	1 - 100
40-6	97	1 - 100
40-7	95	101 - 1200
41	92	101 - 1200
42	92	101 - 1200
43	98	1 - 100
44	99	1 - 100
45	98	1 - 100
46	100	1 - 100
47	97	1 - 100
48	96	1 - 100
49	98	1 - 100

Example No.	% inhibition of PDE9A2 (at 10 micromolar concentration)	IC_{50} within range [nanomolar (nM)]
50	97	1 - 100
51	96	1 - 100
52	100	1 - 100
53	99	1 - 100
54	97	1 - 100
55	97	1 - 100
56	95	1 - 100
57	100	1 - 100
58	96	1 - 100
60	97	1 - 100
61	97	1 - 100
62	95	1 - 100
63	92	101 - 1200
64	97	1 - 100
65	97	1 - 100
66	91	101 - 1200
67	95	101 - 1200
68	97	1 - 100
69	99	1 - 100
70	99	1 - 100
71	99	1 - 100
72	91	101 - 1200
73	97	1 - 100
74	95	1 - 100
75	98	1 - 100
76	98	1 - 100
77	89	101 - 1200
78	99	101 - 1200
79	99	1 - 100

Example No.	% inhibition of PDE9A2 (at 10 micromolar concentration)	IC_{50} within range [nanomolar (nM)]
80	94	1 - 100
81	78	101 - 1200
82	100	1 - 100
83	96	1 - 100
84	97	1 - 100
85	99	1 - 100
86	95	101 - 1200
87	86	101 - 1200
88	96	1 - 100
89	95	101 - 1200
90	100	1 - 100
91	99	1 - 100
92	98	1 - 100
93	97	1 - 100
94	96	101 - 1200
95	98	1 - 100
96	99	1 - 100
97	98	1 - 100
98	97	1 - 100
99	96	1 - 100
100	93	101 - 1200
101	98	1 - 100
102	100	1 - 100
103	99	1 - 100
104	95	101 - 1200
105	84	101 - 1200
106	87	101 - 1200
108	89	101 - 1200
111	88	101 - 1200

Example No.	% inhibition of PDE9A2 (at 10 micromolar concentration)	IC_{50} within range [nanomolar (nM)]
112	97	1 - 100
113	92	101 - 1200
114	89	101 - 1200
115	92	101 - 1200
116	93	101 - 1200
117	97	1 - 100
118	89	101 - 1200
119	95	1 - 100
120	95	1 - 100
121	94	101 - 1200
122	85	101 - 1200
123	91	101 - 1200
124	95	101 - 1200
125	95	1 - 100
126	98	1 - 100
127	97	1 - 100
128	99	1 - 100
129	99	1 - 100
130	99	1 - 100
131	97	1 - 100
132	90	101 - 1200
132-1	97	1 - 100
132-2	100	1 - 100
132-3	89	101 - 1200
132-4	98	1 - 100
132-5	100	1 - 100
132-6	99	1 - 100
132-7	94	1 - 100
132-8	94	101 - 1200
132-9	95	101 - 1200
133	98	1 - 100
134	99	1 - 100
135	98	1 - 100
136	100	1 - 100
137	99	1 - 100
138	100	1 - 100
139	99	1 - 100
140	100	1 - 100
141	99	1 - 100
142	98	1 - 100
143	100	1 - 100
144	100	1 - 100
145	84	101 - 1200
146	91	101 - 1200
147	99	1 - 100
147-1	86	101 - 1200
147-2	87	101 - 1200
147-3	95	1 - 100
148	86	101 - 1200
149	95	101 - 1200
150	90	101 - 1200
151	92	101 - 1200
152	93	101 - 1200
153	90	101 - 1200
154	100	1 - 100
155	100	1 – 100
156	99	1 – 100
157	97	1 - 100

Example No.	% inhibition of PDE9A2 (at 10 micromolar concentration)	IC_{50} within range [nanomolar (nM)]
158	97	1 - 100
159	100	1 - 100
160	96	1 - 100
161	95	101 - 1200
162	98	1 - 100
163	97	101 - 1200
164	98	101 - 1200
165	99	101 - 1200
166	92	101 - 1200
167	93	101 - 1200
168	90	101 - 1200
169	86	101 - 1200
170	75	101 - 1200
171	100	101 - 1200
172	100	1 - 100
173	86	101 - 1200
174	89	101 - 1200
175	88	101 - 1200
176	85	101 - 1200
177	93	101 - 1200
178	92	101 - 1200
179	91	101 - 1200
180	96	101 - 1200
181	96	1 - 100
182	100	1 - 100
183	99	1 - 100
184	97	1 - 100
185	100	1 - 100
186	97	1 - 100

Example No.	% inhibition of PDE9A2 (at 10 micromolar concentration)	IC_{50} within range [nanomolar (nM)]
187	96	1 - 100
188	96	1 - 100
189	90	101 - 1200
190	82	101 - 1200
191	92	101 - 1200
192	100	101 - 1200
193	99	101 - 1200
194	97	101 - 1200
195	88	101 - 1200
196	91	101 - 1200
197	91	101 - 1200
198	100	101 - 1200
199	88	101 - 1200
200	91	101 - 1200
201	85	101 - 1200
202	83	101 - 1200
203	84	101 - 1200
204	87	101 - 1200
205	100	1 - 100
206	82	101 - 1200
207	100	1 - 100
208	100	101 - 1200
209	89	101 - 1200
210	97	1 - 100
211	99	1 - 100
212	92	101 - 1200
213	86	101 - 1200
214	98	1 - 100
215	93	101 - 1200

Example No.	% inhibition of PDE9A2 (at 10 micromolar concentration)	IC_{50} within range [nanomolar (nM)]
216	96	1 - 100
217	97	101 - 1200
218	88	101 - 1200
219	100	1 - 100
220	100	1 - 100
221	100	1 - 100
222	100	1 - 100
223	100	1 - 100
224	100	1 - 100
225	100	1 - 100
226	100	1 - 100
227	100	1 - 100
228	100	1 - 100

Example No.	% inhibition of PDE9A2 (at 10 micromolar concentration)	IC_{50} within range [nanomolar (nM)]
229	99	1 - 100
230	100	1 - 100
230-1	98	1 - 100
230-2	100	1 - 100
230-3	99	1 - 100
230-4	98	101 - 1200
231	95	1 - 100
232	99	1 - 100
233	100	1 - 100
234	100	1 - 100
235	98	101 - 1200
236	93	101 - 1200
237	89	101 - 1200

In vivo effect:

The in vivo effect of the compounds of this invention can be tested in the Novel Object Recognition test according to the procedure of Prickaerts *et al.* (*Neuroscience*; **2002**, *113*, 351-361).

For further information concerning biological testing of the compounds of the present invention see also *Neuropharmacology*, **2008**, *55*, 908-918.

CHEMICAL MANUFACTURE

Abbreviations:

APCI *Atmospheric pressure chemical ionization*

DAD *diode array detector*

DMSO *dimethyl sulphoxide*

ESI *electrospray ionization (in MS)*

Exp. *example*

Fp. *melting point*

h *hour(s)*

HPLC *high performance liquid chromatography*

HPLC-MS *coupled high performance liquid chromatography with mass spectrometric detection*

GC-MS *gas chromatography with mass spectrometric detection*

MPLC *medium pressure liquid chromatography*

mL *millilitre*

µL *microlitre*

min *minutes*

MS *mass spectrometry*

racem. *racemic*

rt *room temperature*

R_t *retention time (in HPLC)*

Rf *retardation factor (in TLC)*

TBTU *2-(1 H-Benzotriazole-1-yl)-1,1,3,3-Tetramethyluronium tetrafluoroborate*

TFA *trifluoroacetic acid*

TLC *thin-layer chromatography*

LC-MS methods:

Method A

Instrument: HPLC/MS ThermoFinnigan. HPLC Surveyor DAD, LCQduo Ion trap.; column: Sunryse MS-C18, 5 um, 4.6x100 mm; eluent A: water + 20 mM ammonium formate; eluent B: acetonitrile + 20 mM ammonium formate; gradient: A/B (95:5) for 1 min, then to A/B (5:95) in 7 min for 1.5 min; flow rate: 0.85 mL/min; UV detection: 254 nm; ion source: ESI

Method 1

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Varian Microsorb 100 C18, 30 x 4.6 mm, 3.0 µm; eluent A: water + 0.13 % TFA, eluent B: acetonitrile; gradient: 0.0 min 5 % B → 0.18 min 5 % B → 2.0 min 98 % B → 2.2 min 98 % B → 2.3 min 5 % B → 2.5 min 5 % B; flow rate: 3.5 mL/min; UV detection: 210-380 nm.

Method 2

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Merck Chromolith Performance RP18e, 100 x 1 mm; eluent A: water + 0.13 % TFA, eluent B: acetonitrile; gradient: 0.0 min 5 % B → 0.2 min 5 % B → 1.6 min 98 % B → 1.9 min 98 % B → 2.0 min 5 % B → 2.2 min 5 % B; flow rate: 3.5 mL/min; UV detection: 210-380 nm.

Method 1D

Instrument:HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Sunryse MS-C18, 5 um, 4.6 x 100 mm; eluent A: 90 % water +10 % acetonitrile + ammonium formate 10 mM; eluent B: acetonitrile 90 % + 10 % water + ammonium formate 10 mM; gradient:A (100) for 1 min, then to B (100) in 7 min for 1 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI.

Method 1E

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Symmetry C8, 5 µm, 3 x 150 mm; eluent A: 90 % water + 10 % acetonitrile + ammonium formate 10 mM; eluent B: acetonitrile 90 % + 10 % H_2O + ammonium formate 10 mM; gradient: A (100) for 1.5 min, then to B (100) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI

Method 1E fusion

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Synergi Fusion-RP80A, 4 µm, 4.60 x 100 mm; eluent A: 90 % water + 10 % acetonitrile + ammonium formate 10mM; eluent B: acetonitrile 90 % + 10 % H_2O + ammonium formate 10 mM; gradient: A (100 %) for 1.5 min, then to B (100 %) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI

Method 1E hydro

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Synergi Hydro-RP80A, 4 µm, 4.60 x 100 mm; eluent A: 90 % water + 10 % acetonitrile + ammonium formate 10 mM; eluent B: acetonitrile 90 % + 10 % H_2O + ammonium formate 10 mM; gradient: A (100 %) for 1.5 min, then to B (100 %) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI

Method 2F

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, Finnigan LCQduo Ion trap; column: Symmetry-C18, 5 um, 3 x 150 mm; eluent A: 95 % water + 5 % acetonitrile + formic acid 0.1 %; eluent B: acetonitrile 95 % + 5 % water + formic acid 0.1 %; gradient: A/B (95/5) for 1.5 min, then to A/B (5/95) in 10 min for 1.5 min; flow rate: 1 mL/min; UV detection: 254 nm; ion source: ESI

Method 2L

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, Finnigan LCQduo Ion trap;

column: Symmetry Shield, 5 um, 4,6 x 150 mm; eluent A: 90 % water + 10 % acetonitrile + formic acid 0.1 %; eluent B: acetonitrile 90 % + 10 % water + formic acid 0.1 %; flow rate: 0,85 mL/min; UV detection: 254 nm; ion source: ESI

Method Grad_C8_acidic

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C8, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A/B (80:20), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 mL/min; UV detection: 254 nm; ion source: ESI

Method Grad_C18_acidic

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Sunfire MS-C18, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A/B (80:20), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate:1.3 mL/min; UV detection: 254 nm; ion source: ESI.

Method Grad_90_10_C8_acidic

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C8, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A (100 %), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 mL/min; UV detection: 254 nm; ion source: ESI.

Method Grad_90_10_C18_acidic

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C18, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A (100), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate:1.3 mL/min; UV detection: 254 nm; ion source: ESI.

Method Grad_C8_NH_4COOH

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole. Column: Xterra MS-C8, 3.5 µm, 4.6 x 50 mm; eluent A: water + ammonium formate 5 mM + 10 % acetonitrile; eluent B: acetonitrile; gradient: A 100 %, then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 mL/min; UV detection: 254 nm; ion source: ESI.

Chiral HPLC Methods

Instrument: Agilent 1100. Column: Chiralpak AS-H Daicel, 4.6 µm, 4.6 x 250 mm;

Method Chiral 1: eluent: hexane/ethanol 97/3 (isocratic); flow rate: 1.0 mL/min; UV detection: 254 nm.
Method Chiral 2: eluent: hexane/ethanol 98/2 (isocratic); flow rate: 1.0 mL/min; UV detection: 254 nm
Method Chiral 3: eluent: hexane/ethanol 80/20 (isocratic); flow rate: 1.0 mL/min; UV detection: 254 nm

GC/MS methods

Method 3A

Instrument: GC/MS Finnigan. Trace GC, MSQ quadrupole. Column: DB-5MS, 25 m x 0.25 mm x 0.25 µm; carrier gas: helium, 1 mL/min constant flow; oven program: 50°C (hold 1 minute), to 100°C in 10°C/min, to 200°C in 20°C/min, to 300°C in 30°C/min eluent, detection: trace MSQ, quadrupole
ion source: IE scan range: 50-450 u.

Method 3A.1

Instrument: GC/MS Finnigan Thermo Scientific. Trace GC Ultra, DSQ II single quadrupole. Column: DB-5MS UI, 25 m x 0.25 mm x 0.25 µm; carrier gas: helium, 1 mL/min constant flow; oven program: 50°C (hold 1 minute), to 100°C in 10°C/min, to 200°C in 20°C/min, to 300°C in 30°C/min eluent, detection: trace DSQ, single quadrupole

Microwave heating:

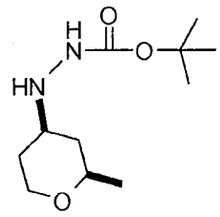
Microwave apparatus types:

- Discover® CEM instruments, equipped with 10 and 35 mL vessels;
- Microwave apparatus type: Biotage Initiator Sixty.

General comment concerning the presentation of the structures

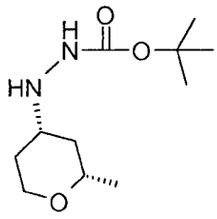
Some compounds have one or more chiral centres. The depicted structure will not necessarily show all the possible stereochemical realisation of the compound but only one. However, in such cases a term like "cis-racemic mixture" is depicted next to the structure in order to point to the other stereochemical options.

An example is given for Example 7D, below. The presented structural formula is



Cis - racemic mixture

The added term "cis - racemic mixture" points to the second stereochemical option:



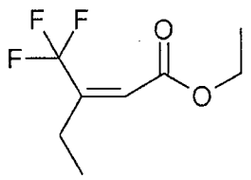
This principle applies to other depicted structures as well.

Synthesis

In the following the manufacture of compounds which exemplify the present invention is described. In case the process of manufacture of a specific compound has not been disclosed literally, the skilled person in the art will find a description of analogue procedures within these descriptions which he can follow in principle. At some places it is said, the examples can be prepared in analogy to another example. If reference should be made to such an "analogue process" the reactions conditions are about the same, even if molar ratios of reagents and educts might to be adjusted. It also will be evident that starting materials within a described process can be varied chemically to achieve the same results, i.e. if a condensation reaction of an ester is described, in that the alcoholic component is a leaving group but not subject of the product, this alcoholic component may vary without significant changes of the procedure as such.

Starting compounds:

Example 1A

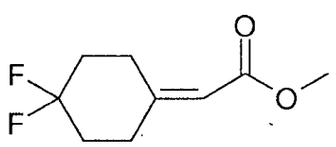


A solution of 70 g (201 mmol) carbethoxymethylene triphenylphosphorane in 300 mL diethyl ether was cooled to 0°C and 25 g (198 mmol) 1.,1,1-trifluorobutanone was added. The solution was warmed to room temperature and stirred over night. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure (700 mbar and 40°C bath temperature). The residue was purified by vacuum distillation (170 mbar and 130°C bath temperature, main fraction: 95-96°C). 29 g (75 %) of the product were obtained as colourless oil.

HPLC-MS (Method 1): R_t: 1.77 min

MS (ESI pos): m/z = 196 $(M+H)^+$

Example 1AA



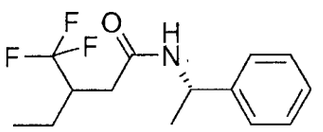
400 mg (10.0 mmol) sodium hydride (60 % in mineral oil) was suspended in 10 ml THF and cooled to 4°C. While being stirred, a solution of 1.3 ml (8.99 mmol) trimethylphosphono acetate in 10 ml THF was added. The mixture was stirred for 1 h at the same temperature. After this, a solution of 4,4-difluorocyclohexanone in 10 ml THF was added at 0°C. The mixture was allowed to warm to room temperature and stirred for 14 h. THF and water was added and the THF evaporated. The remainder was diluted with ethyl acetate, washed with water and saturated sodium hydrogen carbonate solution and evaporated to yield 1.49 g (95 %) of the product.

MS (EI): m/z = 190 $(M)^+$

The following examples 1B, 1C, 1D, 1E, 2A, 2B, 2C and 2D show how the racemic acids 3-trifluoromethyl-pentanoic acid and 3-trifluoromethyl-butyric acid can be transferred into the two enantiomeric forms of the free acid. The resolution can be done via separation of diastereomeric intermediates. The two pure enantiomeric forms of the free acid will be called enantiomer A, enatiomer B respectively. The corresponding diastereomeric intermediates will be called diastereomer A, diastereomer B respectively.

The same principle may be applied for enantiomeric resolution of other racemic mixtures if appropriate.

Example 1B



Diastereoisomer A

A solution of racemic 3-trifluoromethyl-pentanoic acid (8 g, 47 mmol), TBTU (16.6 g, 52 mmol) and diisopropylethylamine (24.1 mL, 141 mmol) in dimethylformamide (80 mL) was stirred at 20°C for 1h then (*S*)-(−)-1-phenylethylamine (10 g, 82 mmol) was added and the mixture was stirred for 16 h at 20°C. The solvent was removed and dichloromethane (200 mL) was added. The resulting mixture was washed with citric acid 10 % in water (200 mL), K_2CO_3 20 % in water (100 mL) and dried over sodium sulphate. Evaporation of the solvent gave a crude solid that was mixed with methanol (10 mL) and filtered through a pad of activated basic alumina. Separation of diastereoisomers was obtained by flash chromatography on SiO_2 eluting with a mixture of cyclohexane/ethyl acetate 85/15.

4.5 g (35.8 %) of the title compound were obtained as white solid.

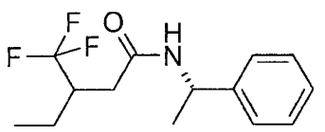
Rf: 0.25 (cyclohexane/ethyl acetate 85/15, stained with basic $KMnO_4$)

HPLC-MS (Method 1E hydro): R_t: 9.35 min

MS (APCI pos): m/z = 274 $(M+H)^+$.

Chiral HPLC (Method Chiral 1): R_t: 5.58 min de: >99 %

Example 1C



Diastereoisomer B

4.4 g (34.2 %) of a white solid were obtained as second product from flash chromatography of Example 1B.

Rf: 0.20 (cyclohexane/ethyl acetate 85/15, stained with basic $KMnO_4$)

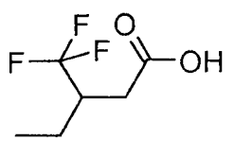
HPLC-MS (Method 1E hydro): R_t: 9.33 min

MS (APCI pos): m/z = 274 $(M+H)^+$.

Chiral HPLC (Method Chiral 1): R_t: 6.18 min de: >99 %

Example 1D

3-Trifluoromethyl-pentanoic acid, Enantiomer A



Enantiomer A

A solution of Example 1B (4.6 g, 17 mmol) in dioxane (15 mL) was treated with H_2SO_4 70 % in water (25 mL) and refluxed for 16 h. The mixture was cooled, basified to pH 14 with NaOH 32 % in water, diluted with water (50 mL) and extracted with

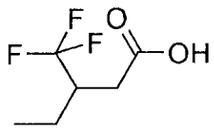
dichloromethane (2x 200 mL). The resulting solution was acidified to pH 1 with 9N HCl, extracted with dichloromethane (3x 500 mL) and the combined organic phases were dried. Evaporation of solvent afforded 2.47 g (86.3 %) of a brown oil.

Rf: 0.66 (dichloromethane/methanol 9/1, stained with Bromocresol Green)

Chiral HPLC (Method Chiral 1): R_t 5.58 min ee: >99 %

Example 1E

3-Trifluoromethyl-pentanoic acid, Enantiomer B



Enantiomer B

In analogy to the preparation of Example 1D, the title compound was obtained using Example 1C as starting material.

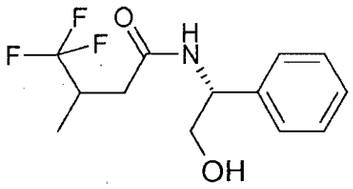
Yield: 80.3 %

Rf: 0.66 (dichloromethane/methanol 9/1, stained with Bromocresol Green)

Chiral HPLC (Method Chiral 1): R_t: 5.08 min ee: >99 %

Example 2A

4,4,4-Trifluoro-N-((R)-2-hydroxy-1-phenyl-ethyl)-3-methyl-butyramide, Diastereoisomer A



A solution of 3-(trifluoromethyl)butyric acid (10 g, 64 mmol) in dimethylformamide (100mL) was treated with N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (14.7 g, 77 mmol), 4-dimethyl-amino pyridine (11 g, 89.7 mmol) and

(R)-(-)-phenylglycinol (9.9 g, 70.5 mmol). The mixture was stirred at 20°C for 16h, then concentrated to reduce the volume and treated with 10 % citric acid in water (300 mL). The mixture was extracted with ethyl ether (2x 200mL) and the separated organic phase were washed with 10 % $NaHCO_3$ (150 mL) and brine (150 mL). The organic phase was dried and evaporated to give 13.1 g of a crude white solid.

Separation of diastereoisomers was achieved by flash chromatography on SiO_2 eluting with a mixture of ethyl acetate/hexane 6/4.

5.32g (30.2 %) of the title compound were obtained as white solid.

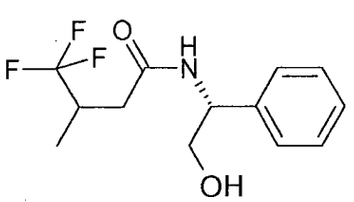
Rf: 0.23 (ethyl acetate/hexane 6/4)

HPLC-MS (1E hydro): R_t: 6.97 min

MS (APCI pos): m/z = 276 $(M+H)^+$.

Example 2B

4,4,4-Trifluoro-N-((R)-2-hydroxy-1-phenyl-ethyl)-3-methyl-butyramide, Diastereoisomer B



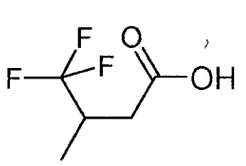
3.08 g (17.5 %) of a white solid were obtained as second product from flash chromatography of Example 2A.

Rf: 0.16 (ethyl acetate/hexane 6/4)

HPLC-MS (1E hydro): R_t: 6.92 min

MS (APCI pos): m/z = 276 $(M+H)^+$.

Example 2C, Enantiomer A



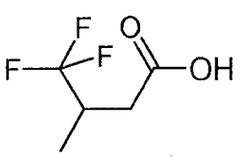
A solution of Example 2A (2 g, 7.26 mmol) in tetrahydrofuran (10 mL) was treated with H_2SO_4 70 % in water (10 mL) and refluxed for 16 h. The mixture was cooled, basified to pH 14 with NaOH 32 % in water, diluted with water (50 mL) and extracted with dichloromethane (2x 50mL). The resulting solution was acidified to pH 1 with 9N HCl, extracted with dichloromethane (3x 50 mL) and the combined organic phases were dried. Evaporation of solvent afforded 0.84 g (74.1 %) of a brown oil.

HPLC-MS (1E hydro): R_t: 1.73 min

MS (APCI neg): m/z = 155 $(M-H)^-$.

Chiral HPLC (Method Chiral 2): R_t: 6.92 min ee: 99 %

Example 2D, Enantiomer B



In analogy to the preparation of Example 2C, the title compound was obtained using Example 2B as starting material. Obtained 1.4 g (8.96 mmol)

Yield: 82.3 %

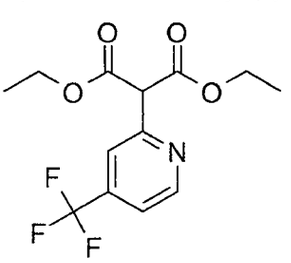
HPLC-MS (1E hydro): R_t: 1.30 min

MS (APCI neg): m/z = 155 $(M-H)^-$.

Chiral HPLC (Method Chiral 2): R_t: 6.49 min ee: 98.6 %

Example 3A

2-(4-Trifluoromethyl-pyridin-2-yl)-malonic acid diethyl ester



A suspension of sodium hydride 60 % in mineral oil (1.65 g, 41 mmol) in anhydrous dioxane (36 mL) was treated with diethylmalonate (6.3 mL, 41 mmol) at 25°C and heated to 60°C for 30 min. Cuprous chloride (1.63 g, 17 mmol) was added, the mixture was heated to 80°C and 2-chloro-4-(trifluoromethyl)-pyridine was added and the was heating increased to 100°C for 16h.

After cooling to 20°C the mixture was acidified with 37 % HCl, diluted with water (120 mL) and extracted with dichloromethane (2 x 60 mL). The organic phase was dried and evaporated to give a crude oil that was purified by flash chromatography eluting with n-hexane/ethyl acetate from 95/5 to 60/40.

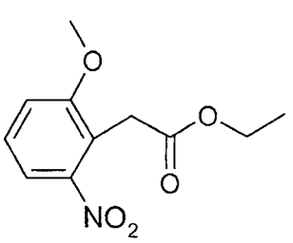
1.9 g (38 %) were obtained as a colourless oil.

HPLC-MS (2F): R_t: 12.24 min

MS (ESI pos): m/z = 306 $(M+H)^+$.

Example 4A

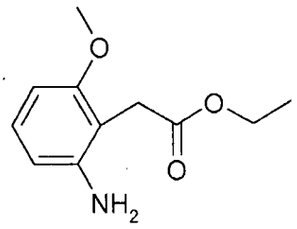
The following example was synthesized in analogy to the preparation of Example 5U, using the corresponding acid (Sinova Inc., Bethesda, MD 20814, USA) as starting material.



HPLC-MS (Method 1): R_t: 1.47 min

MS (ESI pos): m/z = 194 $(M+H-EtOH)^+$

Example 4B



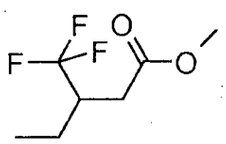
2.0 g (8.6 mmol) of Example 4A was dissolved in 40 mL ethanol, Pd (10 % on charcoal) was added, and the mixture was hydrogenated at room temperature (2h, 50 psi). The reaction mixture was filtered and the residue washed with ethanol. The solvent was evaporated by reduced pressure.1.80 g (100 %) of the product were obtained.

HPLC-MS (Method 1): R_t: 0.91 min

MS (ESI pos): m/z = 210 $(M+H)^+$

Example 5A

3-Trifluoromethyl-pentanoic acid methyl ester, Enantiomer A



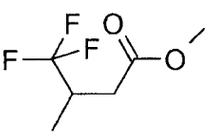
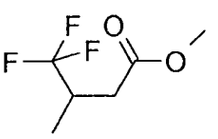
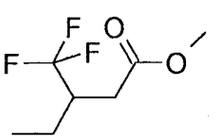
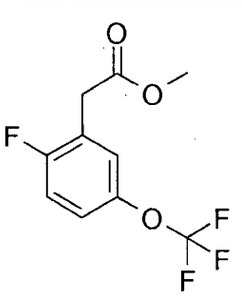
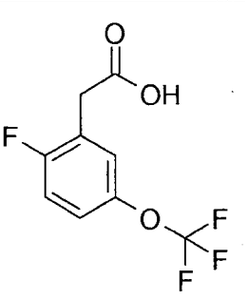
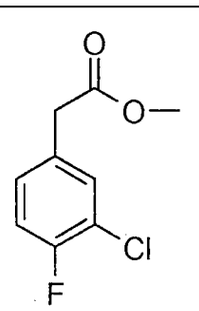
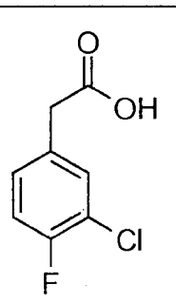
Enantiomer A

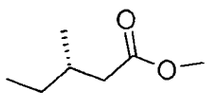
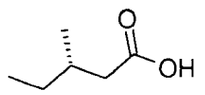
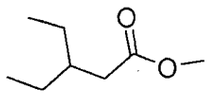
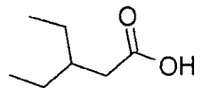
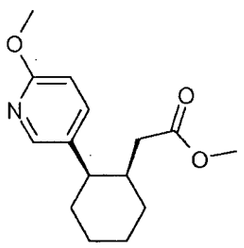
To a stirred solution of Example 1D (250 mg, 1.47 mmol) in dichloromethane (10 mL) and methanol (0.25 mL), under nitrogen atmosphere, trimethylsilyldiazomethane (2.0 M solution in diethyl ether) (2.1 mL, 4.19 mmol) was added drop wise at 0°C. The reaction mixture was stirred keeping the temperature below 5°C for 1h. The solvent was removed (40°C, 25 bar) yielding 250 mg (75.4 %) of a yellow oil that was used in the next step without further purification.

GC (Method 3A): R_t: 3.29 min

MS (EI): m/z: 165 $(M-19)^+$,155 $(M-29)^+$, 153 $(M-31)^+$

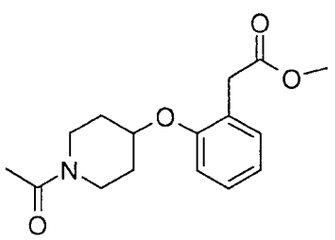
The following examples were synthesized in analogy to the preparation of Example 5A, using the corresponding acids as starting materials:

	structure	starting material: carboxylic acid	R_t [min]	MS *m/z*
Example 5B Enantiomer A		Example 2C	8.01 (Method 3A)	170 [EI]
Example 5 C Enantiomer B		Example 2D	8.01 (Method 3A)	170 [EI]
Example 5D Enantiomer B		Example 1E	3.29 (Method 3A)	165(M-19)$^+$, 155(M-29)$^+$, 153(M-31)$^+$ [EI]
Example 5E			7.82 (Method 3A)	252 [EI]
Example 5F			9.53 (Method 3A)	202 [EI]

	structure	starting material: carboxylic acid	R_t [min]	MS *m/z*
Example 5G Enantio-mer S			3.92 (Method 3A)	130 [EI]
Example 5H			5.09 Method 3A	115 $(M-29)^+$ [EI]
Example 5HA cis, racem. mixture		Example 18A	1.22 (Method 1)	264 [ESI, $(M+H)^+$]

Example 5I

[2-(1-Acetyl-piperidin-4-yloxy)-phenyl]-acetic acid methyl ester



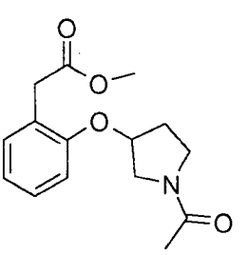
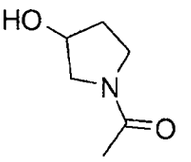
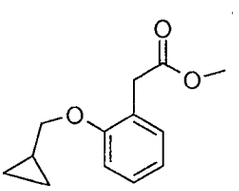
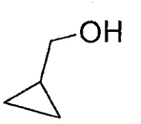
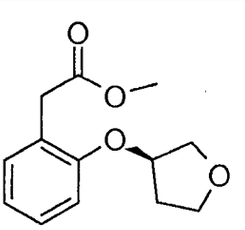
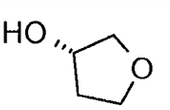
Di-tert-butylazodicarboxylate (305 mg, 1.32 mmol) was dropped to a solution of 1-(4-hydroxy-piperidin-1-yl)-ethanone (259 mg, 1.8 mmol) in tetrahydrofuran (4 mL) under nitrogen atmosphere. Then (2-hydroxy-phenyl)-acetic acid methyl ester (200 mg, 1.2 mmol) and triphenylphosphine (347 mg, 1.3 mmol) were added. The yellow mixture was stirred at 20°C for 16h. The solvent was evaporated and the residue was purified

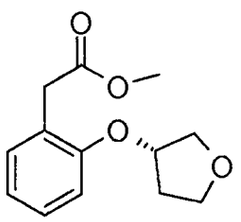
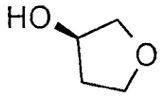
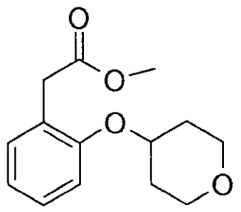
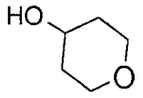
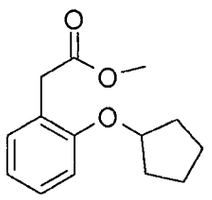
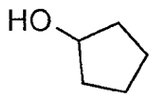
on silica using hexane/ethyl acetate mixture of increasing polarity (from 70 % to 100 % ethyl acetate) as eluent to give 195 mg (55.6 %) of a colourless oil.

HPLC-MS (Method Grad_C8_NH_4COOH): R_t: 2.67 min

MS (ESI pos): m/z = 292 $(M+H)^+$.

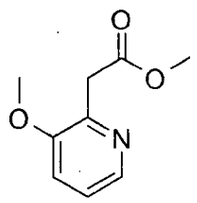
The following examples were synthesized in analogy to the preparation of Example 5G, using the corresponding alcohols as starting materials:

	Structure	starting material: Alcohol	Rf	R_t [min]	MS m/z
Example 5J racem. mixture				2.53 (Method Grad_C8_ NH_4COOH)	292 $(M+H)^+$
Example 5K			0.35 (hexane/ethyl acetate 8/2)		
Example 5L			0.2 (hexane/ethyl acetate 7/3)		

	Structure	starting material: Alcohol	Rf	R_t [min]	MS m/z
Example 5M			0.2 (hexane/ethyl acetate 7/3)		
Example 5O			0.25 (hexane/ethyl acetate 7/3)		
Example 5P			0.35 (hexane/ethyl acetate)		

Example 5Q

(3-Methoxy-pyridin-2-yl)-acetic acid methyl ester



A mixture of (3-methoxy-2-pyridin-2-yl) acetonitrile (400 mg, 2.7 mmol) in 2 mL of methanol and 96 % sulphuric acid (1.8 mL, 32 mmol) was heated in a microwave oven at 120°C for 1h. The mixture was cooled to 0°C, basified with solid $NaHCO_3$,

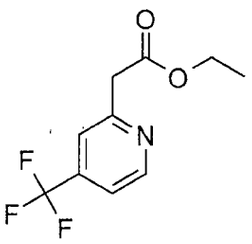
diluted with water (2mL) and extracted with dichloromethane. The separated organic phase was dried and evaporated to give 450 mg (92 %) of a dark yellow oil that was used in the next step without further purification.

HPLC-MS (Method Grad_C8_NH_4COOH): R_t: 1.92 min

MS (ESI pos): m/z = 182 $(M+H)^+$.

Example 5R

(4-Trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester



A solution of Example 3A (1.0 g, 3.27 mmol) in anhydrous DMSO (8 mL) was treated with water (60 microL, 3.27 mmol) and lithium chloride (347 mg, 8.2 mmol). The resulting mixture was heated at 120°C for 16h. After cooling to 20°C the mixture was treated with brine (12 mL) and extracted with ethyl acetate (3x 20 mL). The organic phase was dried and evaporated to give a crude oil that was purified by flash chromatography eluting with n-hexane/ethyl acetate 8/2.

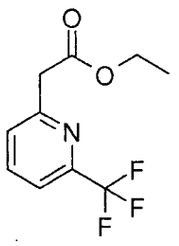
390 mg (51 %) were obtained as a colourless oil.

HPLC-MS (Method 2F): R_t: 11.09 min

MS (ESI pos): m/z = 234 $(M+H)^+$

Example 5S

(6-Trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester



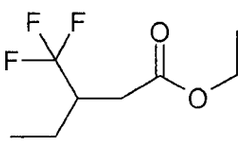
A mixture of caesium carbonate (1.87g, 5.75 mmol) and tri-t-butylphosphine (107 µL, 0.44 mmol) in dry 1,2 dimethoxyethane (10 mL) was treated with tris-(dibenzylideneacetone)di-palladium (81 mg, 0.09 mmol), 2-Bromo-6-(trifluoromethyl)pyridine (1g, 4.42 mmol) and diethylmalonate (0.8 mL, 5.3 mmol) under nitrogen atmosphere. The mixture was heated to 150°C for 30 min in a microwave oven. After cooling to 20°C the mixture was treated with a saturated solution of ammonium chloride (120 mL) and extracted with ethyl ether (3x 80mL). The organic phase was dried and evaporated to give a crude oil that was purified by flash chromatography eluting with n-hexane/ethyl ether 6/1.

460 mg (81 %) were obtained as a colourless oil.

GC (Method 3A): R_t: 8.28 min

MS (EI): m/z = 233 $(M)^+$

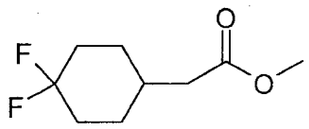
Example 5T, racemic mixture



29 g (148 mmol) of Example 1A was combined with 2 g Pd/C (10 %) and hydrogenated at room temperature (6h, 15 psi). The reaction mixture was filtered and washed with diethyl ether. The solvent was evaporated under reduced pressure (500 mbar, 40°C bath temperature). 27.6 g (94 %) of the product were obtained as a colourless liquid.

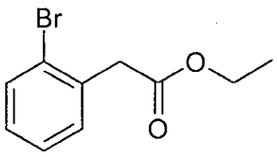
HPLC-MS (Method 1): R_t: 1.65 min

Example 5TA



1.49 g (95 %, 7.43 mmol) was dissolved in 20 ml ethanol and hydrogenated over 150 mg Pd/C (10 %) at atmospheric pressure for 14 h. The mixture was filtered and the solvent removed to yield 1.27 g (89 %) of the product.

Example 5U

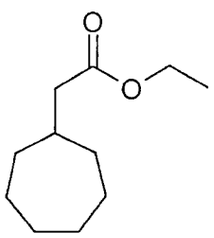
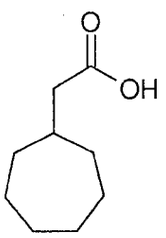
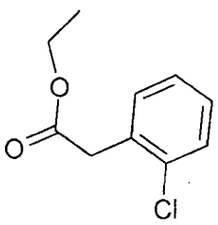
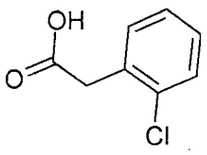
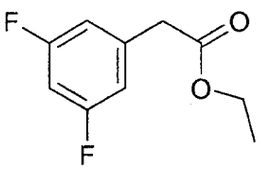
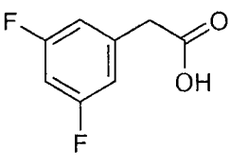
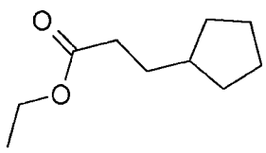
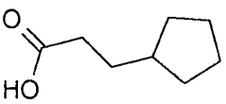
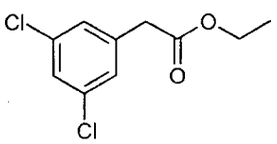
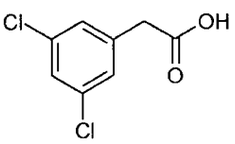
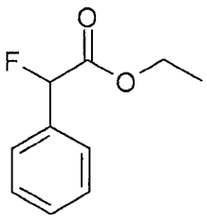
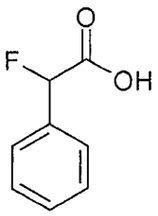


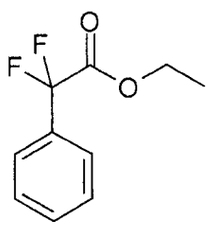
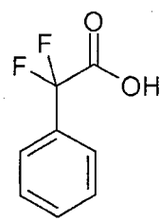
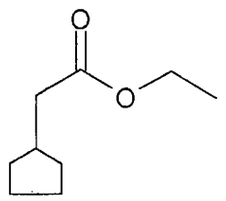
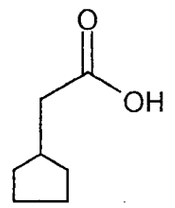
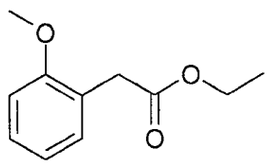
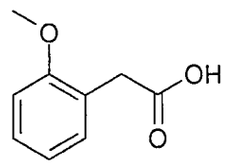
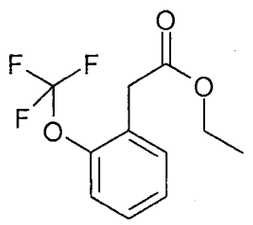
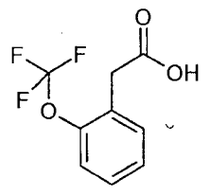
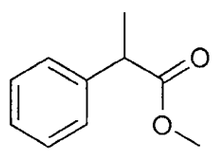
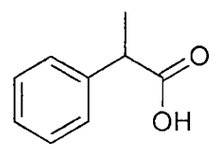
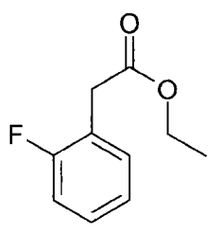
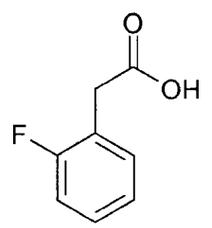
A solution of 15 g (69.8 mmol) of (2-bromo-phenyl)-acetic acid in 50 mL ethanol was cooled to 0°C and 8 mL (110 mmol) thionylchloride was added drop wise. The reaction mixture was heated to 50°C over night. After cooling to room temperature the solvent was removed under reduced pressure. The residue was mixed with ethyl acetate and filtered over 30 g basic aluminium oxide. The filtrate was evaporated under reduced pressure. 18 g (92 %) of the product were obtained.

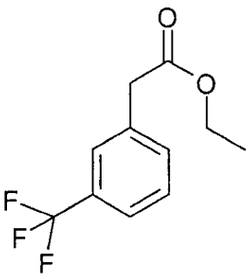
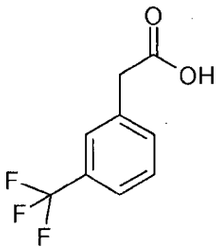
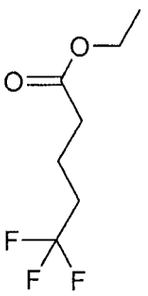
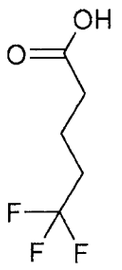
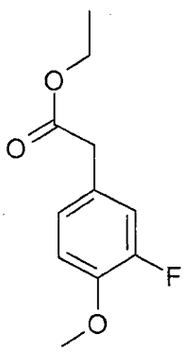
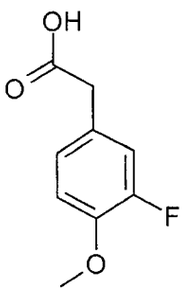
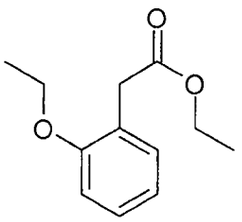
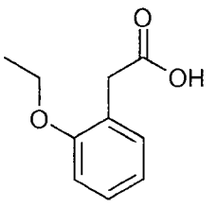
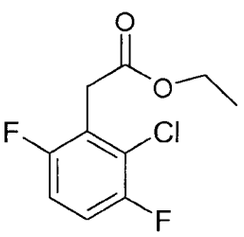
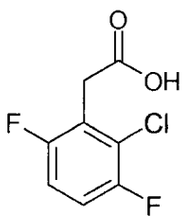
HPLC-MS (Method1): R_t: 1.62 min

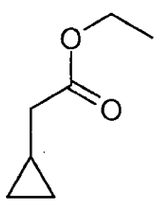
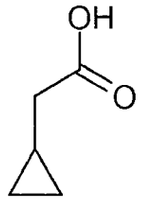
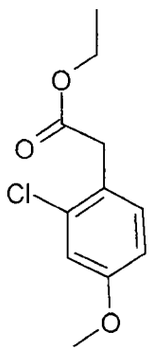
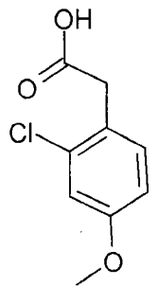
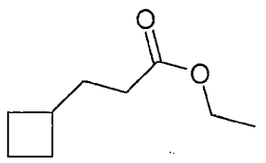
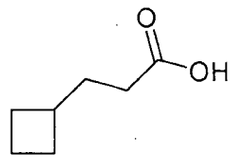
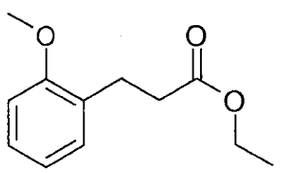
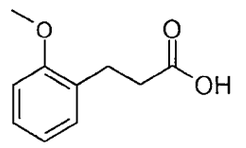
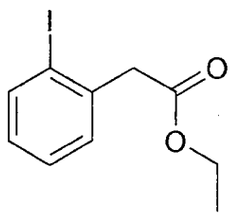
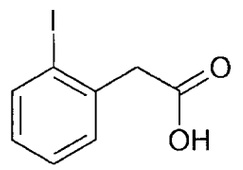
MS (ESI pos): m/z = 243/45 (Br) $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 5U, using the corresponding acids as starting materials.

	structure	starting material	R_t [min]	MS (ESI m/z)
Exp. 5V				185 $(M+H)^+$
Exp. 5Y			1.56 (Method 1)	199/201 (Cl) $(M+H)^+$
Exp. 5W			1.53 (Method 1)	201 $(M+H)^+$
Exp. 5X				171 $(M+H)^+$
Exp. 5Z			1.74 (Method 1)	233/235/237 (2Cl) $(M+H)^+$
Exp. 5AA racem. mixture				133 $(M+H)^+$

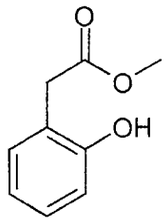
Exp. 5AB				201 $(M+H)^+$
Exp. 5AC			1.65 (Method 1)	157/58 $(M+H)^+$
Exp. 5AD			1.36 (Method 1)	195 $(M+H)^+$
Exp. 5AE			1.69 (Method 1)	249/50 $(M+H)^+$
Exp. 5AF racem. mixture				commerciall y available
Exp. 5AG			1.46 (Method 1)	

Exp. 5AH			1.63 (Method 1)	
Exp. 5AI				185 $(M+H)^+$
Exp. 5AJ			1.43 (Method 1)	213 $(M+H)^+$
Exp. 5AK				
Exp. 5AL			1.58 (Method 1)	235/237 (Cl) $(M+H)^+$

Exp. 5ALA			1.29 (Method 1)	129 $(M+H)^+$
Exp. 5ALB			1.54 (Method 1)	229/231 (Cl) $(M+H)^+$
Exp. 5ALC			1.62 (Method 1)	157 $(M+H)^+$
Exp. 5ALD			1.56 (Method 1)	209 $(M+H)^+$
Exp. 5ALE			1.59 (Method 1)	291 $(M+H)^+$

Example 5AM

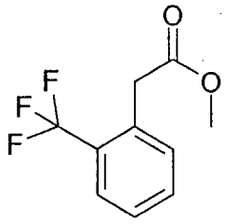
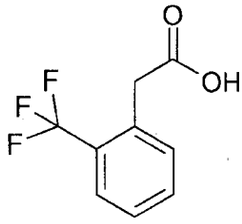
The following example was synthesized in analogy to the preparation of Example 5U, using the corresponding acid as starting material and methanol as solvent.



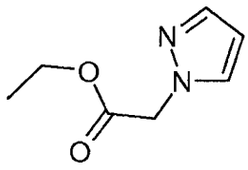
HPLC-MS (Method 1): R_t: 1.04 min

MS (ESI pos): m/z = 167 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 5AM, using the corresponding acids as starting materials.

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 5AMA			1.52 (Method 1)	236 $(M+NH_4)^+$

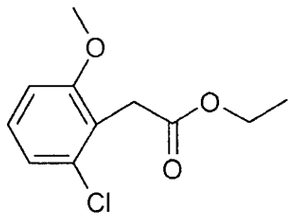
Example 5AN



6.0 g (88.5 mmol) pyrazole was dissolved in 60 mL DMSO and 10.4 g (93 mmol) potassium-tert-butylate was added in portions, keeping the temperature between 20-25°C. The reaction mixture stirred 10 min at room temperature. 10.8 mL (98 mmol) ethyl bromacetate was added drop wise, keeping the temperature between 25-35°C. The reaction mixture was stirred for 2h at room temperature. The reaction mixture was added to a saturated aqueous solution of NaCl and extracted with ethyl acetate. The organic layer was dried, filtered, and the filtrate was evaporated under reduced

pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane / methanol 95/5).10.4 g (38 %) of the product were obtained.

Example 5AO

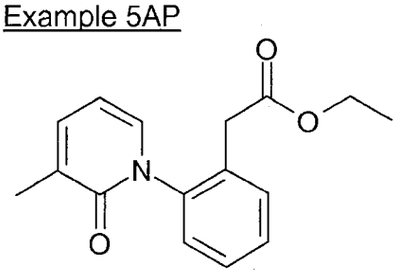


1.83 g (7.7 mmol) of Example 4B was mixed with in 60 mL 4N HCl and cooled with an ice bath. A solution of 1.15 g (16.4 mmol) sodium nitrite in 13.5 mL water was added drop wise. After 10 min a solution of 3.9 g (39.5 mmol) copper(I)chloride in 20 mL conc. HCl was added drop wise. The reaction mixture was allowed to turn to room temperature and stirred for 30 min. The mixture was extracted with ethyl acetate. The organic layer was neutralized with potassium carbonate, filtered over celite and the filtrate extracted with water. The organic layer was dried, filtered and the filtrate was evaporated under reduced pressure. 1.24 g (62 %) of the product were obtained.

HPLC-MS (Method 1): R_t: 1.60 min

MS (ESI pos): m/z = 229/231 (Cl) $(M+H)^+$

Example 5AP



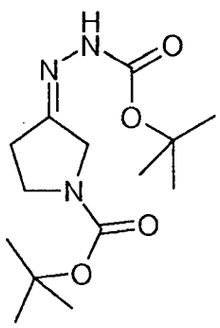
Under argon 1.00 g (4.11 mmol) of example 5U, 540 mg (4.95 mmol) 3-methylpyridone and 80 mg (0.42 mmol) copper-(I) iodide were mixed with 5 ml DMSO and 1.14 g (8.25 mmol) potassium carbonate and 120 mg (0.82 mmol) 8-hydroxyquinoline were added. The mixture was stirred for 48 h at 120°C. After

cooling to room temperature the mixture was dissolved in ethyl acetate and washed with 1 M HCl and saturated sodium chloride solution. The organic phase was separated, dried and evaporated. The residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). The acetonitrile was evaporated and the remainder extracted with ethyl acetate. The organic phase was dried and evaporated to yield 633 mg (57 %) of the desired product.

HPLC-MS (Method 1): R_t: 1.56 min

MS (ESI pos): m/z = 272 $(M+H)^+$

Example 6A



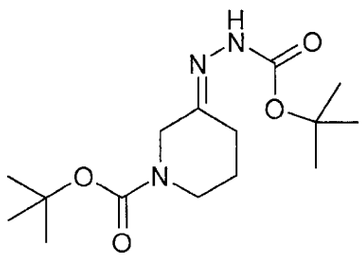
10 g (54 mmol) 1-N-Boc-3-pyrrolidinone was dissolved in 50 mL ethanol and 7.3 g (55.2 mmol) tert-butyl carbazate was added. The reaction mixture was stirred at room temperature for 2h. The solvent was evaporated by reduced pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane / methanol 95/5). 18 g (89 %) of the product were obtained as oil.

HPLC-MS (Method 1): R_t: 1.35 min

MS (ESI neg.): m/z = 298 $(M-H)^-$

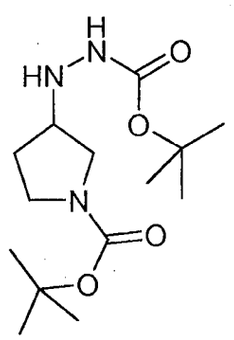
Example 6B

The following example was synthesized in analogy to the preparation of Example 6A, using 1-N-Boc-3-piperidone as starting material.



HPLC-MS (Method 1): R_t: 1.45 min

Example 7A, racemic mixture

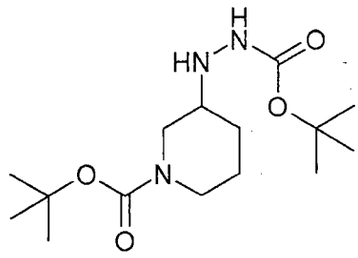


18 g (48 mmol) of Example 6A was dissolved in 300 mL methanol, 2.5 g Pd/C (10 %) was added, and the mixture was hydrogenated at room temperature (8h, 50 psi). The reaction mixture was filtered and the residue washed with methanol. The solvent was evaporated by reduced pressure. 16 g of product were obtained as a colourless oil and used without further purification.

HPLC-MS (Method 1): R_t: 1.36 min

Example 7B, racemic mixture

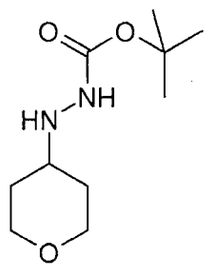
The following example was synthesized in analogy to the preparation of Example 7A, using Example 6B as starting material.



HPLC-MS (Method 1): R_t: 1.42 min

MS (ESI pos): m/z = 316 $(M+H)^+$

Example 7C

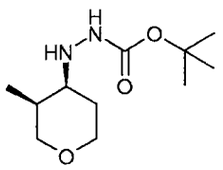
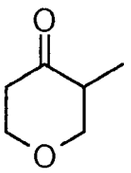
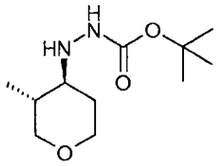
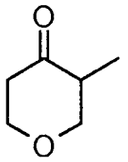
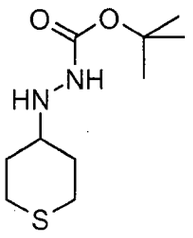
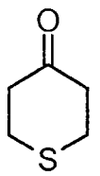


10 g (100 mmol) of tetrahydropyran-4-one was dissolved in 100 mL methanol and 14.5 g (110 mmol) tert-butylcarbazate was added. The reaction mixture was stirred at room temperature for 2h. The solvent was evaporated by reduced pressure. The residue was mixed with 140 mL acetic acid (50 %), 6.9 g (110 mmol) sodium cyanoborohydride was added and the mixture was stirred at room temperature over night. The reaction mixture was neutralized with 4M NaOH and extracted with dichloromethane. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and a saturated aqueous solution of sodium chloride.

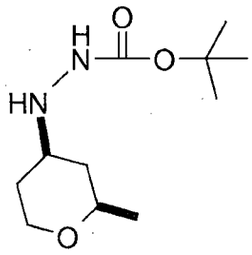
The organic layer was dried over sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure. 19 g (88 %) of the product were obtained as a white solid.

MS (ESI pos): m/z = 217 $(M+H)^+$

The following example was synthesized in analogy to the preparation of Example 7C using the corresponding keton as starting material.

	Structure	starting material: keton	R_t [min]	MS m/z
Example 7CA cis, racem. mixture			11.12 (Method 3A)	174 [EI, $(M-56)^+$]
Example 7CB trans, racem. mixture			11.22 – (Method 3A)	174 [EI, $(M-56)^+$]
Example 7CC			0.99 (Method 1)	177 [ESI, $(M-56+H)^+$]

Example 7D



Cis - racemic mixture

A solution of 2-methyl-tetrahydro-pyran-4-one (2.2 g, 19.7 mmol) in methanol (30 mL) was treated with tert-butyl carbazate (2.6 g, 19.7 mmol) and stirred for 3h at 20°C. Evaporation of solvent affords a white solid that was mixed with 30 mL acetic acid (50 % in water), and treated with sodium cyanoborohydride (1.2 g, 19.7 mmol) portion wise. The mixture was stirred at 20°C for 16h then neutralized with 5N NaOH and extracted with dichloromethane. The organic phase was washed with a saturated solution of $NaHCO_3$ and brine, dried, filtered and evaporated to give a crude solid. Separation of diastereoisomers was obtained by flash chromatography on SiO_2 eluting with a mixture of cyclohexane/ethyl acetate mixture of increasing polarity (from 7/3 to 1/1) to give 1.85 g (41 %) of a white solid.

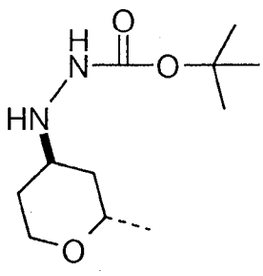
Rf: 0.29 (hexane/ethyl acetate 1:1)

HPLC-MS (Method Grad_90_10_C8_acidic): R_t: 1.79 min

MS (ESI pos): m/z = 131 $(M-100+H)^+$

The cis configuration between methyl and carbazyl group was implied by the ROESY correlation for H-2/H-4.

Example 7E



Trans - Racemic mixture

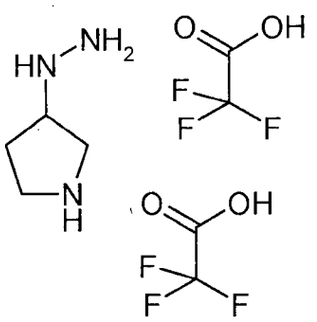
0.7 g (16 %) of a colourless oil were obtained as the second product from flash chromatography of Example 7D

Rf: 0.29 (hexane/ethyl acetate 1:1 stained with Pancaldi's reagent)

HPLC-MS (Method Grad_90_10_C8_acidic): R_t: 1.96 min

MS (ESI pos): m/z = 131 $(M-100+H)^+$

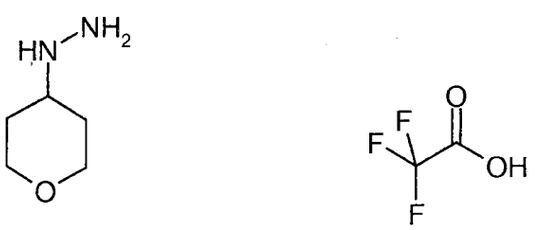
Example 8A, racemic mixture



14 g (46.5 mmol) of Example 7A were dissolved in 50 mL dichloromethane, cooled with an ice bath and 25 mL (325 mmol) trifluoroacetic acid was added. The reaction mixture was stirred 3h at room temperature. The solvent was evaporated under reduced pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane / methanol 8/2). 12 g (78 %) of the product were obtained.

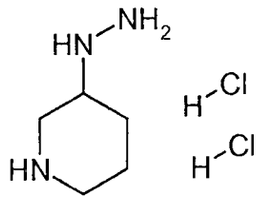
Example 8B

The following example was synthesized in analogy to the preparation of Example 8A, using Example 7C as starting material.



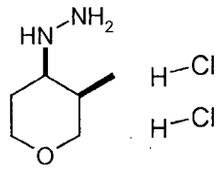
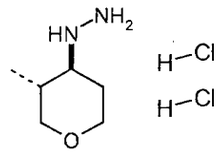
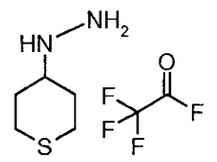
MS (ESI pos): m/z = 117 $(M+H)^+$

Example 8C, racemic mixture

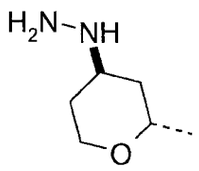


13.0 g (37.1 mmol) of Example 7B were dissolved in 5 mL dioxane and 93 mL (371 mmol) of hydrochloride acid in dioxane (4 M) were added. The reaction mixture was stirred over night at room temperature. 40 mL diethyl ether were added and the mixture stirred 15 min at room temperature. The reaction mixture was filtered. 7.0 g (100 %) of the product were obtained as white solid.

The following examples were synthesized in analogy to the preparation of example 8C using the corresponding Boc-hydrazine as starting material.

	Structure	starting material: Boc-hydrazine	MS m/z
Example 8CA cis, racem. mixture		Example 7CA	131 $(M+H)^+$
Example 8CB trans, racem. mixture		Example 7CB	131 $(M+H)^+$
Example 8CC		Example 7CC	133 $(M+H)^+$

Example 8D



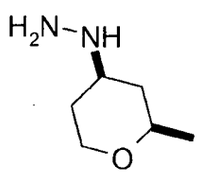
trans - racemic mixture

A solution of Example 7E (700mg, 3 mmol) in dioxane (5 mL) was treated with 4N HCl in dioxane (15 mL, 60 mmol) and the mixture stirred at 20°C for 18h. The solvent was evaporated to give 560 mg (91 %) of a sticky solid that was used in the next step without further purification.

HPLC-MS (Grad_C8_NH_4COOH_Lowmass): R_t: 0.67 min

MS (ESI pos): m/z = 131 $(M+H)^+$

Example 8E



cis -racemic mixture

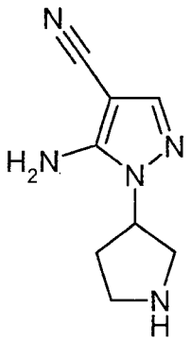
In analogy to the preparation of Example 8D, the title compound was obtained using Example 7D as starting material.

Yield: 68.3 %

HPLC-MS (Method Grad_C8_NH_4COOH_Lowmass): R_t: 0.70 min

MS (ESI pos): m/z = 131 $(M+H)^+$

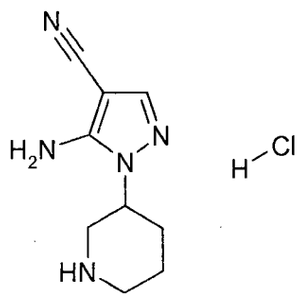
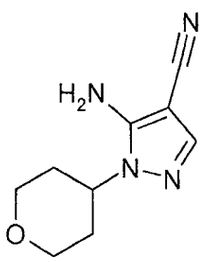
Example 9A, racemic mixture

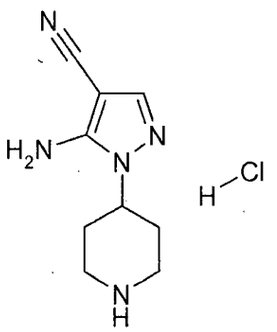
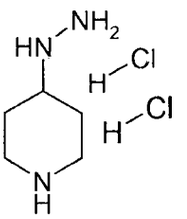
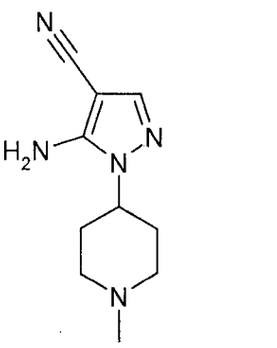
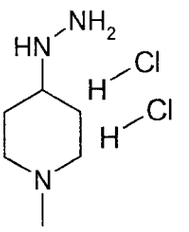
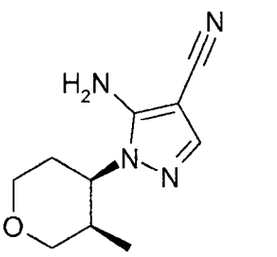
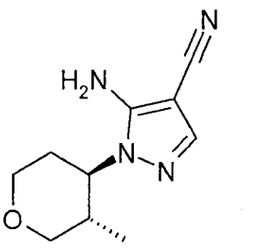
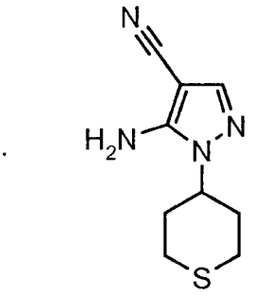


32.0 g (77.8 mmol) of Example 8A was mixed with with 12.0 g (98.3 mmol) of ethoxymethylene-malonodinitrile in 250 mL ethanol, and 40 mL (288 mmol) of triethylamine were added. The reaction mixture was heated to 50°C for 2h. After cooling to room temperature the solvent was removed under reduced pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane / methanol 8/2).

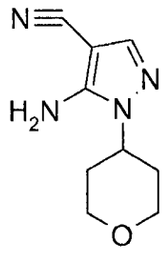
HPLC-MS (Method 1): R_t: 0.29 min

The following examples were synthesized in analogy to the preparation of Example 9A, using the corresponding hydrazines as starting materials.

	structure	starting material	R_t[min]	MS (ESI, m/z)
Exp. 9B racem. mixture		Example 8C	0.59 (Method1)	192 $(M+H)^+$
Exp. 9C		Example 8B	0.76 (Method1)	193 $(M+H)^+$

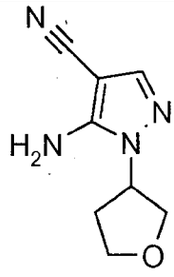
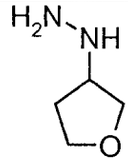
Exp. 9D			0.32 (Method1)	192 $(M+H)^+$
Exp. 9E			0.40 (Method1)	206 $(M+H)^+$
Example 9EA cis, racem. mixture		Example 8CA	1.90 Grad C8-NH_4CCOH	207 $(M+H)^+$
Example 9EB trans, racem. mixture		Example 8CB	1.87 Grad C8-NH_4CCOH	207 $(M+H)^+$
Example 9EC		Example 8CC	1.01 (Method1)	209 $(M+H)^+$

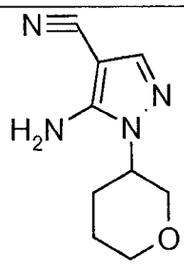
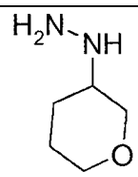
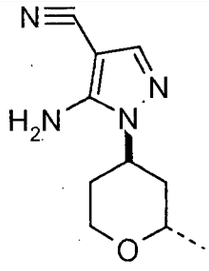
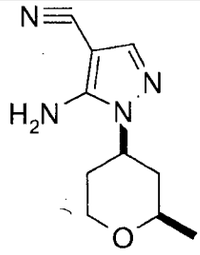
Example 9F



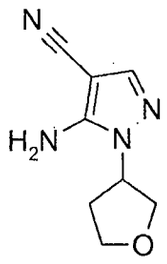
A mixture of 4.4 g (38 mmol) of (tetrahydro-pyran-4-yl)-hydrazine and 4.7 g (38 mmol) of ethoxymethylene-malononitrile in 90 mL of ethanol and 10.5 mL (103 mmol) of triethylamine was stirred at 50°C for 30 min. After cooling to 20°C the solvent was removed under reduced pressure and the residue was treated with a mixture of water / dichloromethane = 1/1. The resulting suspension was stirred for 15 min and then filtered to give a yellow solid that was washed subsequently with dichloromethane, water and dichloromethane. The solid was dried at 45°C under reduced pressure. 2.7 g (37 %) of the title compound were obtained as yellow solid and used in the next step without further purification.

The following examples were synthesized in analogy to the preparation of Example 9F, using the corresponding hydrazines as starting materials:

	Structure	starting material: hydrazine	R_t [min]	MS m/z
Example 9G racem. mixture			1.31 (Method Grad_90_10_C8_acidic)	179 $(M+H)^+$

	Structure	starting material: hydrazine	R_t [min]	MS m/z
Example 9H racem. mixture			4.97 (Method 1E hydro)	193 $(M+H)^+$
Example 9I trans; racem. mixture		Example 8D	2.14 (Method Grad_10_90_C8_acidic)	207 $(M+H)^+$
Example 9J cis; racem. mixture		Example 8E	1.91 (Method Grad_10_90_C8_acidic)	207 $(M+H)^+$

Example 9GA (Enantiomer A)



Enantiomer A

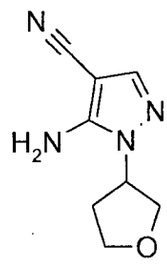
Example 9G was submitted for chiral separation to isolate its enantiomers. The enantiomer labeled A, of unknown but single stereochemistry was isolated using the following conditions.

Amount supplied	5g
Chiral Column	Daicel Chiralpak AD 50 x 300 mm
Mobile phase	n-Hexane (60%)/methyl-tert-butyl ether (40%) /Ethanol (5 %) v/v
Flow rate	20 mL/min
Detection	UV at 254 nm
Injection mode	continuous

Obtained 1g of enantiomer A.

Enantiomeric excess 99.3%; retention time 27.83 min; (analytical method: Chiral 3)

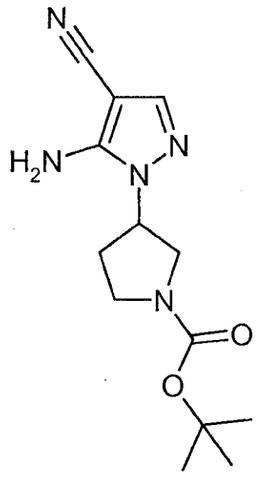
Example 9GB (Enantiomer B)



Enantiomer B

Isolated using the same conditions as enantiomer A, obtaining 0.5 g ; enantiomeric excess 96.7%; R_t:30.94 min; (analytical method: Chiral 3).

Example 10A, racemic mixture

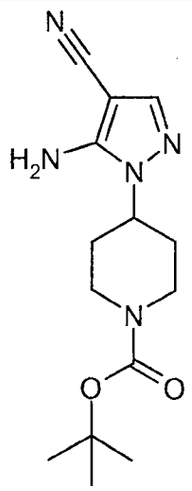
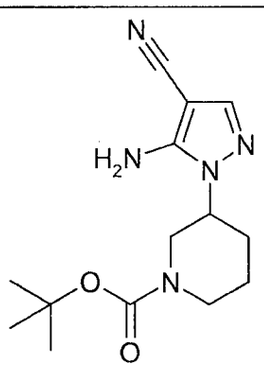


4.0 g (22.6 mmol) of Example 9A were mixed with in 60 mL tetrahydrofuran, and 5.7 g (30 mmol) di-tert-butyl-dicarbamate was added. The reaction mixture was heated to 60°C for 5h. After cooling to room temperature the solvent was removed under reduced pressure. The residue was purified by preparative MPLC (SiO_2, eluent dichloromethane/methanol 9/1).

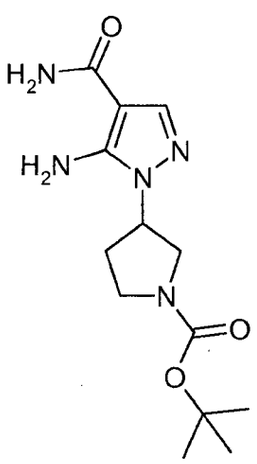
HPLC-MS (Method 1): R_t: 1.28 min

MS (ESI pos): m/z = 278 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 10A, using the corresponding pyrazoles as starting materials.

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 10B		Example 9D	1.30 (Method 1)	292 $(M+H)^+$
Exp. 10C racem. mixture		Example 9B	1.33 (Method 1)	292 $(M+H)^+$

Example 11A, racemic mixture

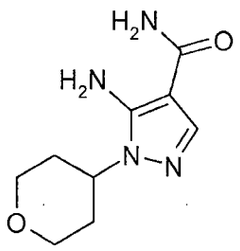
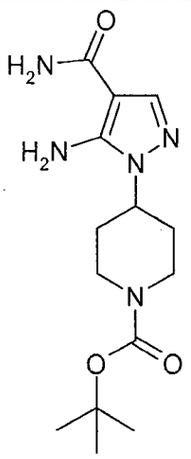


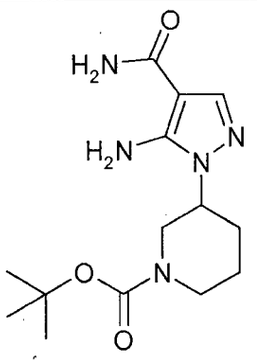
2.4 g (8.96 mmol) of Example 10A were dissolved in 30 mL ethanol. At room temperature a solution of 10 mL (120 mmol) hydrogen peroxide (35 % in water) and 50 mL ammonia (25 % in water) was added slowly over a period of 10 min. The reaction mixture was stirred at room temperature for 2h. The solution was carefully concentrated to a volume of 50 mL under reduced pressure. A precipitate formed and was collected by filtration. 1.3 g (50 %) of the product were obtained as a solid.

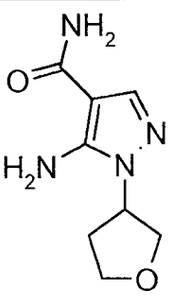
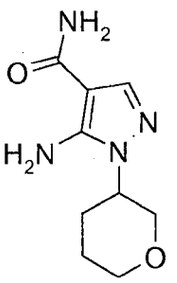
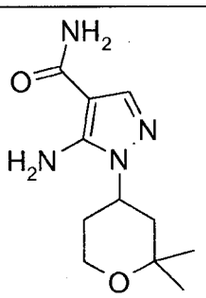
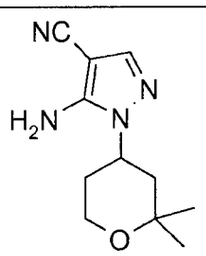
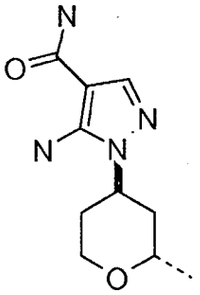
HPLC-MS (Method 1): R_t: 1.08 min

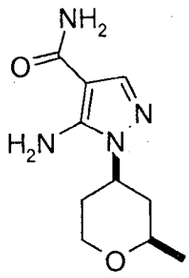
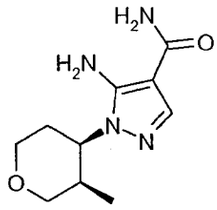
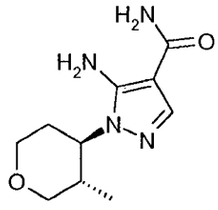
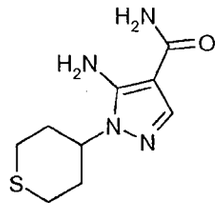
MS (ESI pos): m/z = 296 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 11A, using the corresponding pyrazoles as starting materials.

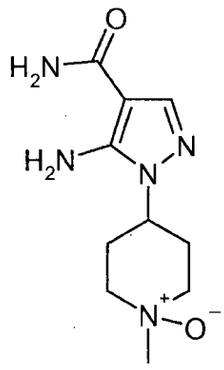
	structure	starting material	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 11B		Example 9C	0.44 (Method 1)	211 $(M+H)^+$
Exp. 11C		Example 10B	1.12 (Method 1)	308 $(M-H)^-$

Exp. 11D racem. mixture		Example 10C	1.13 (Method 1)	310/311 $(M+H)^+$ HPLC-MS

Exp. 11E racem. mixture		Example 9G	2.39 (Method 2F)	197 $(M+H)^+$
Exp. 11F racem. mixture		Example 9H	0.95 (Method Grad_C8_NH$_4$COOH)	211 $(M+H)^+$
Exp. 11G racem. mixture			1.57 (Method Grad_C8_NH$_4$COOH)	339 $(M+H)^+$
Exp. 11H trans, racem. mixture		Example 9I	1.27 (Method Grad_90_10_C8_acidic)	225 $(M+H)^+$

Exp. 11I cis, racem. mixture		Example 9J	1.27 (Method Grad_90_10 _C8_acidic)	225 $(M+H)^+$
Example 11IA cis, racem. mixture		Example 9EA	1.11 (Method Grad_C8_NH 4COOH)	225 $(M+H)^+$
Example 11IB trans, racem. mixture		Example 9EB	1.14 (Method Grad_C8_NH 4COOH)	225 $(M+H)^+$
Example 11IC		Example 9EC		227 $(M+H)^+$

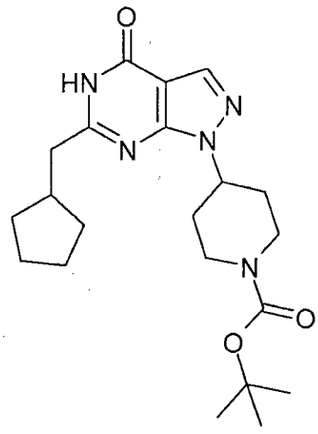
Example 11J, racemic mixture



2.30 g (11.2 mmol) of Example 9E were dissolved in 6 mL dimethylsulfoxide. Under ice cooling 8 mL (77.6 mmol) hydrogen peroxide and 1.7 g (12.3 mmol) potassium carbonate were added. Then the reaction mixture was stirred 15 min at room temperature. The reaction mixture was cooled with an ice bath, 100 mL of water were added and extracted with dichloromethane. The water phase was evaporated under reduced pressure. The residue was mixed with in dichloromethane and filtered. 2.8 g (52 %) of the product were obtained as a white solid.

HPLC-MS (Method1): R_t: 0.24 min

Example 12A



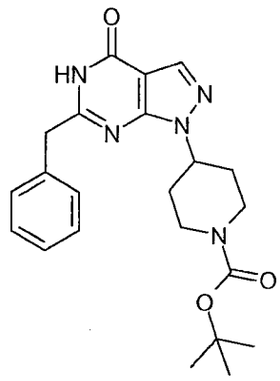
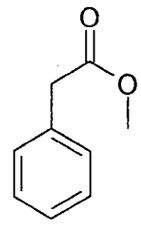
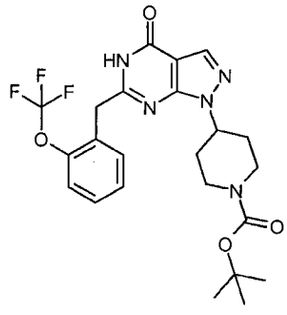
660 mg (2.13 mmol) of Example 11C were dissolved in 15 mL of absolute ethanol. 1.85 g (10.7 mmol) of Example 5AC and 430 mg (10.7 mmol) of sodium hydride (60

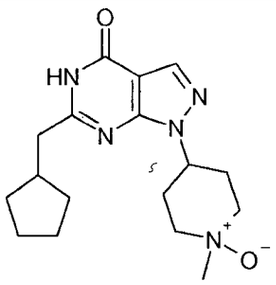
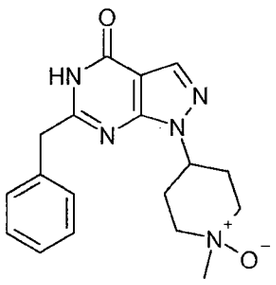
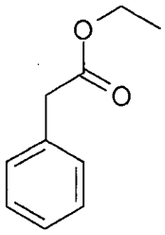
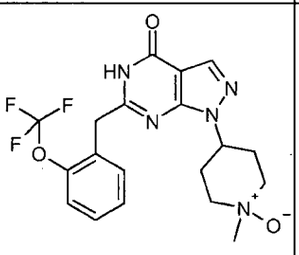
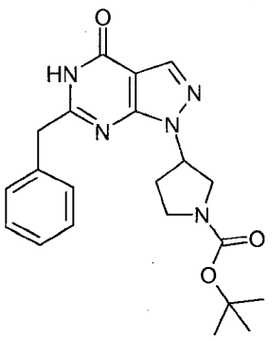
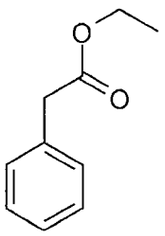
% suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 320 mg (38 %) of the product were obtained as a white solid.

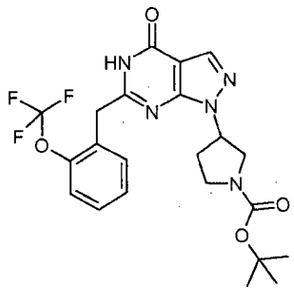
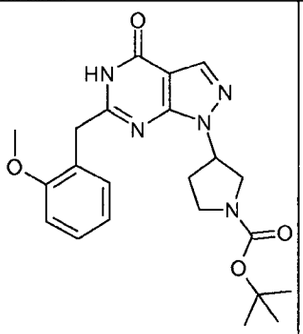
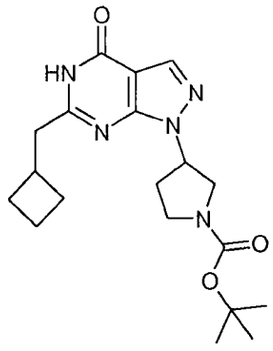
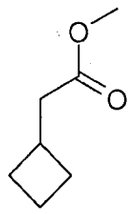
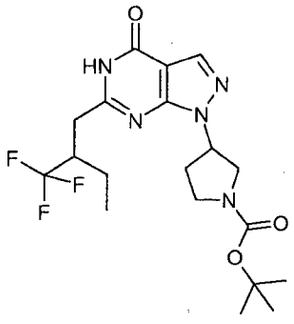
HPLC-MS (Method1): R_t: 1.61 min

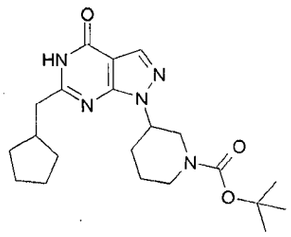
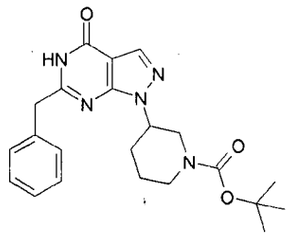
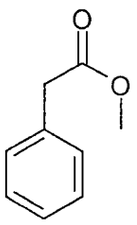
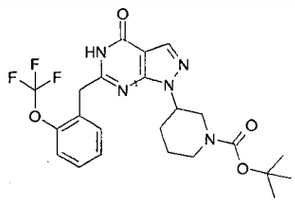
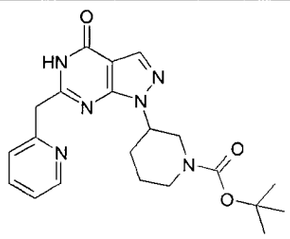
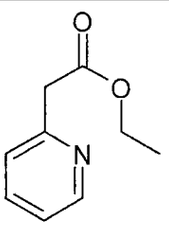
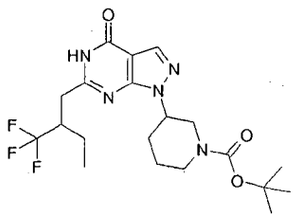
MS (ESI pos): m/z = 402 $(M+H)^+$

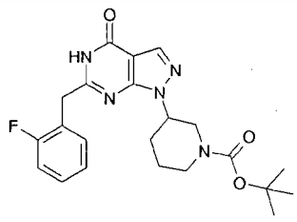
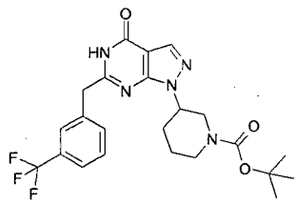
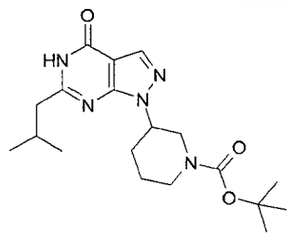
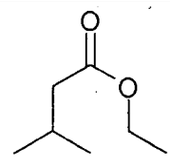
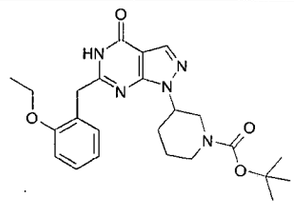
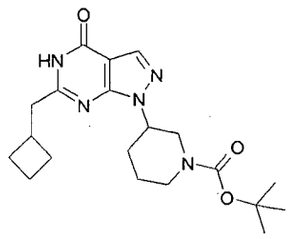
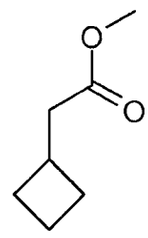
The following examples were synthesized in analogy to the preparation of Example 12A, using the corresponding pyrazoles and esters as starting materials.

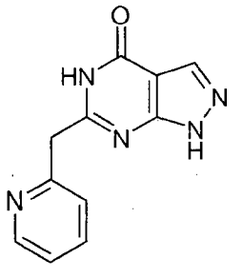
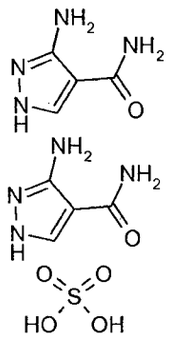
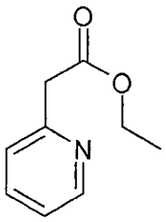
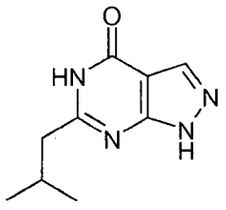
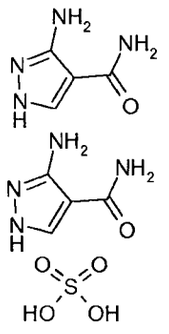
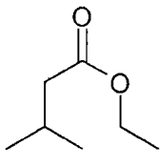
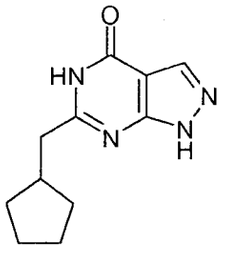
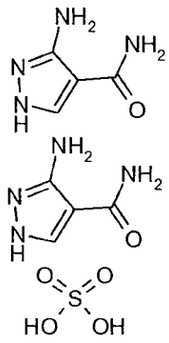
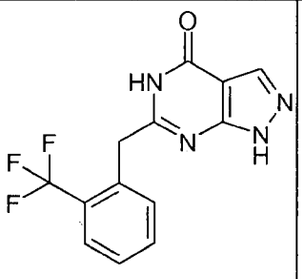
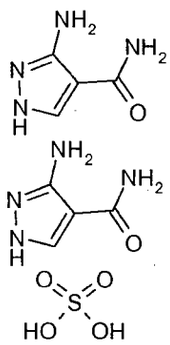
	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12B		Exp. 11C		1.52 (Method 1)	410 $(M+H)^+$
Exp. 12C		Exp. 11C	Example 5AE	1.66 (Method 1)	492 $(M-H)^-$

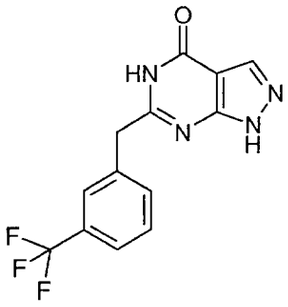
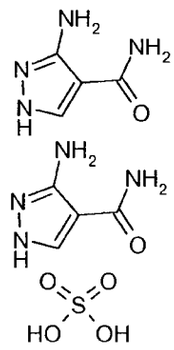
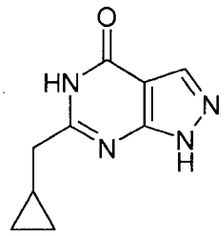
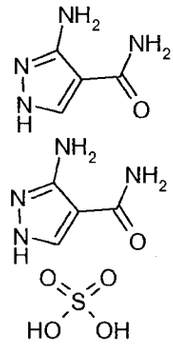
	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12D mixture of stereoisomers		Exp. 11J	Example 5AC	1.02 (Method 1)	332 $(M+H)^+$
Exp. 12E mixture of stereoisomers		Exp. 11J		0.96 (Method 1)	340 $(M+H)^+$
Exp. 12F mixture of stereoisomers		Exp. 11J	Example 5AE	1.12 (Method 1)	424 $(M+H)^+$
Exp. 12G racem. mixture		Exp. 11A		1.49 (Method 1)	396 $(M+H)^+$

	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12H racem. mixture		Exp. 11A	Example 5AE	1.62 (Method 1)	480 $(M+H)^+$
Exp. 12I racem. mixture		Exp. 11A	Example 5AD	1.52 (Method 1)	426 $(M+H)^+$
Exp. 12J racem. mixture		Exp. 11A		1.49 (Method 1)	374 $(M+H)^+$
Exp. 12K mixture of stereoisomers		Exp. 11A	Example 5T	1.58 (Method 1)	428 $(M-H)^-$

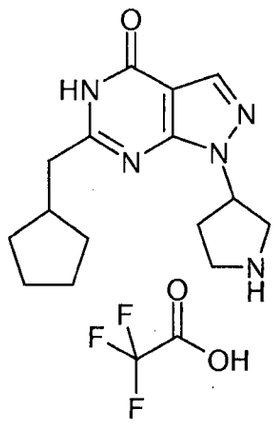
	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12L racem. mixture		Exp. 11D	Example 5AC	1.65 (Method 1)	402 $(M+H)^+$
Exp. 12M racem. mixture		Exp. 11D		1.55 (Method 1)	408 $(M+H)^+$
Exp. 12N racem. mixture		Exp. 11D	Example 5AE	1.67 (Method 1)	494 $(M+H)^+$
Example 12O racem. mixture		Exp. 11D		1.13 (Method 1)	411 $(M+H)^+$
Exp. 12P mixture of stereoisomers		Exp. 11D	Example 5T	1.63 (Method 1)	444 $(M+H)^+$

	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12Q racem. mixture		Exp. 11D	Example 5AG	1.53 (Method 1)	428 $(M+H)^+$
Exp. 12R racem. mixture		Exp. 11D	Example 5AH	1.66 (Method 1)	478 $(M+H)^+$
Exp. 12S racem. mixture		Exp. 11D		1.51 (Method 1)	376 $(M+H)^+$
Exp. 12T racem. mixture		Exp. 11D	Example 5AK	1.63 (Method 1)	454 $(M+H)^+$
Exp. 12U racem. mixture		Exp. 11D		1.56 (Method 1)	388 $(M+H)^+$

	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 12V				1.77 (Method 2F)	228 $(M+H)^+$
Exp. 12W				6.96 (Method 2F)	193 $(M+H)^+$
Exp. 12X			Example 5AC	8.28 (Method 2F)	219 $(M+H)^+$
Exp. 12Y			Example 5AMA	9.15 (Method 2F)	295 $(M+H)^+$

	Structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Example 12Z			Example 5AH	9.54 (Method 2F)	295 $(M+H)^+$
Example 12AA			Example 5ALA	6.48 (Method 2F)	191 $(M+H)^+$

Example 13A, racemic mixture

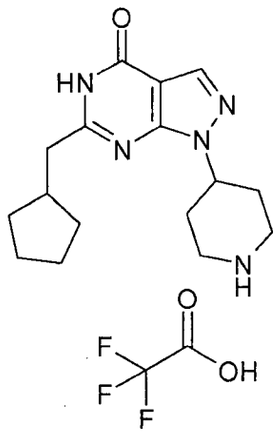


400 mg (1.35 mmol) of Example 11A were dissolved in 8 mL of absolute ethanol, 840 mg (5.4 mmol) of Example 5AC and 220 mg (5.5 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. After cooling to room temperature the reaction mixture was acidified with 4N hydrochloride acid. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 250 mg (46 %) of the product were obtained as a white solid.

HPLC-MS (Method 1): R_t: 0.93 min

MS (ESI pos): m/z = 288 $(M+H)^+$

Example 13B



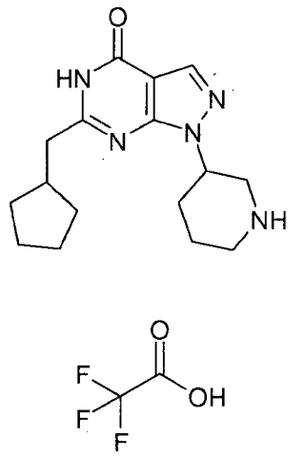
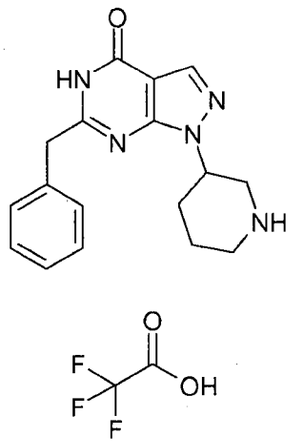
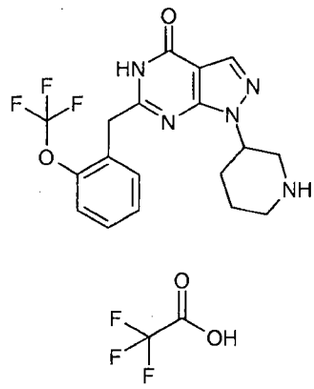
330 mg (0.82 mmol) of Example 12A was dissolved in 3 mL dichloromethane and 1 mL trifluoroacetic acid was added. The reaction mixture was stirred at room temperature over night. The solvent was evaporated under reduced pressure. The remaining product was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 240 mg (70 %) of the product were obtained.

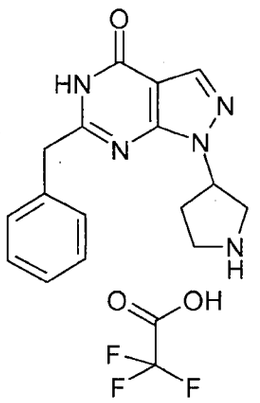
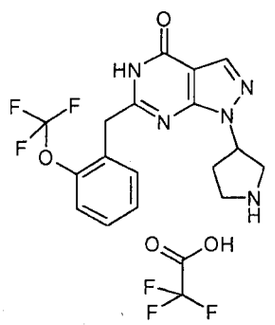
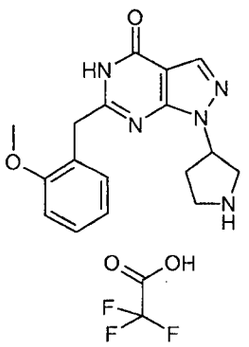
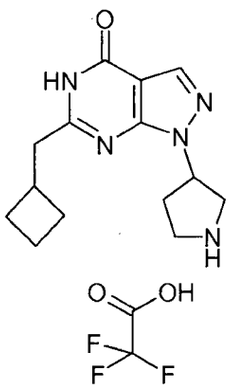
HPLC-MS (Method 1): R_t: 0.96 min

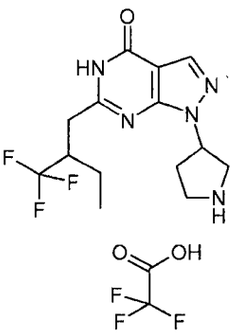
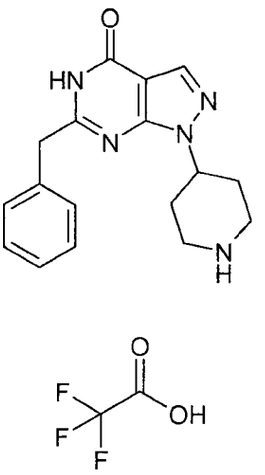
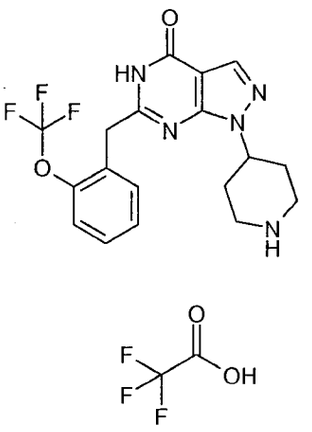
MS (ESI pos): m/z = 302 $(M+H)^+$

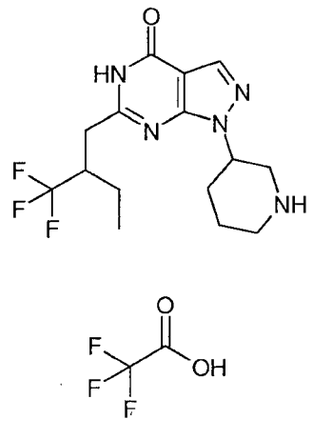
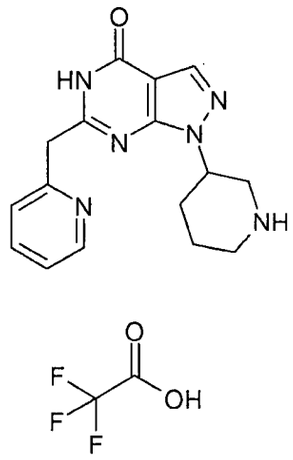
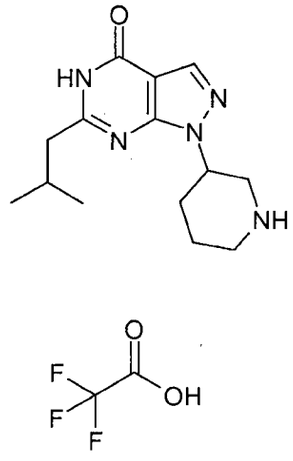
The following examples were synthesized in analogy to the preparation of Example 13B, using the corresponding Boc-protected amines as starting materials

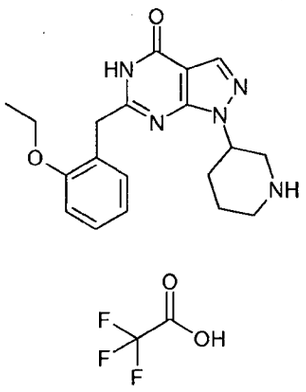
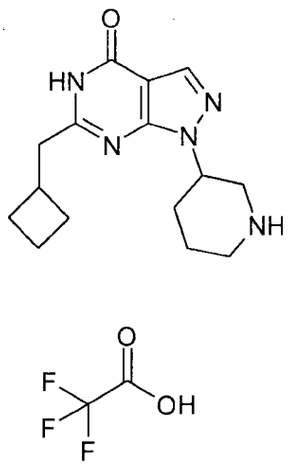
	Structure	starting material	R_t [min]	MS (ESI, m/z)

Exp. 13C racem. mixture		Exp. 12L	1.01 (Method 1)	302 $(M+H)^+$
Exp. 13D racem. mixture		Exp. 12M	0.93 (Method 1)	310 $(M+H)^+$
Exp. 13E racem. mixture		Exp. 12N	1.09 (Method 1)	394 $(M+H)^+$

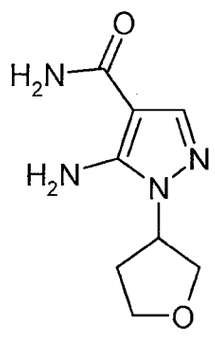
Exp. 13F racem. mixture		Exp. 12G	0.92 (Method 1)	296 $(M+H)^+$
Exp. 13G racem. mixture		Exp. 12H	1.08 (Method 1)	380 $(M+H)^+$
Exp. 13H racem. mixture		Exp. 12I	0.96 (Method 1)	326 $(M+H)^+$
Exp. 13I racem. mixture		Exp. 12J	0.89 (Method 1)	274 $(M+H)^+$

Exp. 13J racem. mixture		Exp. 12K	1.0 (Method1)	330 $(M+H)^+$
Exp. 13K		Exp. 12B	0.92 (Method1)	310 $(M+H)^+$
Exp. 13L		Exp. 12C	1.07 (Method1)	394 $(M+H)^+$

Exp. 13M mixture of stereoisomers		Exp. 12P	1.04 (Method 1)	344 $(M+H)^+$
Exp. 13N racem. mixture		Exp. 12O	0.37 (Method 1)	319 $(M+H)^+$
Exp. 13O racem. mixture		Exp. 12S	0.89 (Method 1)	276 $(M+H)^+$

Exp. 13P racem. mixture		Exp. 12T	1.04 (Method 1)	354 $(M+H)^+$
Exp. 13Q racem. mixture		Exp. 12U	0.94 (Method 1)	288 $(M+H)^+$

Example 15A:



Enantiomer A

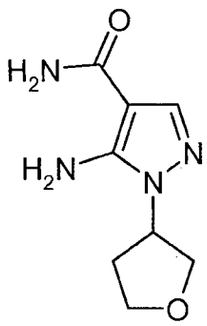
200 mg (1.12 mmol) of Example 9GA was mixed with 4.5 mL ammonia solution (30 % in water). The reaction mixture was heated to 130°C for 30 min in a microwave

oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. 180 mg (82 %) of the product were obtained.

GC-MS (Method 3A. 1): R_t: 12.62 min

$[M]^+$ = 196

Example 16A:



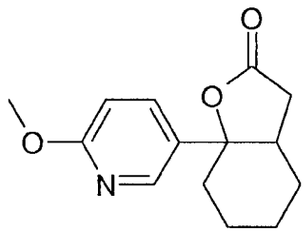
Enantiomer B

150 mg (0.84 mmol) of Example 9GB were mixed with 2.10 mL ammonia solution (30 % in water). The reaction mixture was heated to 130°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. 100 mg (60 %) of the product were obtained.

GC-MS (Method 3A. 2): R_t: 12.59 min

$[M]^+$ = 196

Example 17A, mixture of stereoisomers

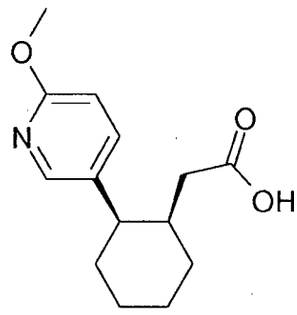


A solution of 1.00 g (5.32 mmol) 2-methoxy-5-bromopyridine in 10 mL anhydrous THF was cooled to -78°C and n-BuLi (3.66 mL, 5.85 mmol, 1.6 M in hexane) was added. After 10 min at -78°C 1.18 g (6.38 mmol) 2-oxo-cyclohexyl-acetic acid ethyl ester was added and the mixture was warmed to 25 °C. Water was added (1 mL) and the mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 370 mg (28 %) of the product were obtained as an oil.

HPLC-MS (Method 1): R_t: 1.23 min

MS (ESI pos): m/z = 248 $(M+H)^+$

Example 18A, cis, racemic mixture



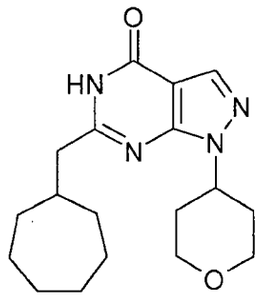
380 mg (1.54 mmol) of Example 17A was mixed with 5 mL methanol, 50 mg Pd/C (10 %) was added, and the mixture was hydrogenated at room temperature (8h, 50 psi). The reaction mixture was filtered and the residue was washed with methanol. The solvent was evaporated under reduced pressure. 340 mg (89 %) of product were obtained as colourless oil and used without further purification.

HPLC-MS (Method 1): R_t: 1.01 min

MS (ESI pos): m/z = 250 $(M+H)^+$

Exemplary embodiments:

Example1



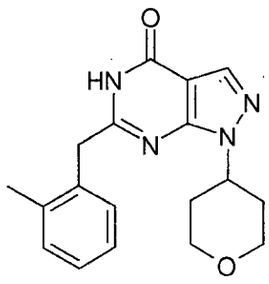
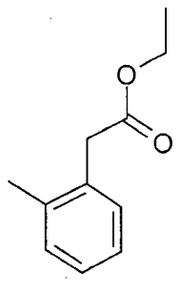
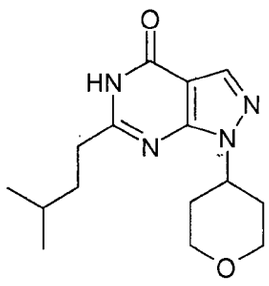
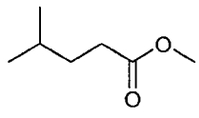
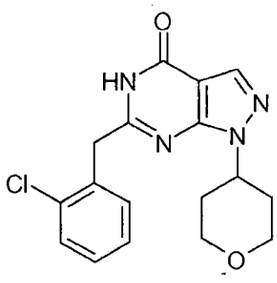
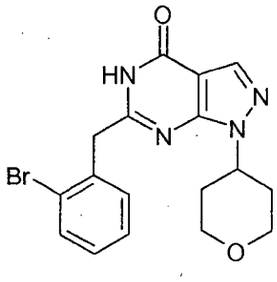
100 mg (0.48 mmol) of Example 11B were dissolved in 5 mL of absolute ethanol, 400 mg (2.17 mmol) of Example 5V and 100 mg (2.5 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 29 mg (18 %) of the product were obtained as a white solid.

HPLC-MS (Method1): R_t: 1.08 min

MS (ESI pos): m/z = 331 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 1, using the corresponding pyrazoles and esters as starting materials

	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)

	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 2		Example 11B		1.27 (Method 1)	325 $(M+H)^+$
Exp. 3		Example 11B		1.22 (Method 1)	291 $(M+H)^+$
Exp. 4		Example 11B	Example 5Y	1.23 (Method 1)	345/347 (Cl) $(M+H)^+$
Exp. 5		Example 11B	Example 5U	1.29 (Method 1)	389/91 (Br) $(M+H)^+$

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

Organizacion y
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SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-121065

2/3

54. **TÍTULO** _____

_____

_____

_____

51. **CLASIFICACIÓN INTERNACIONAL** _____

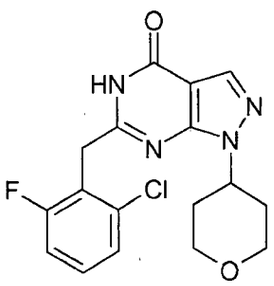
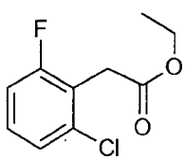
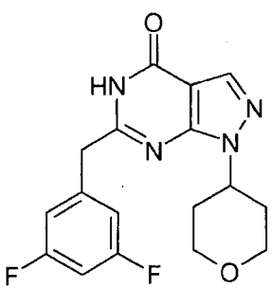
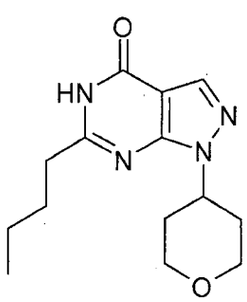
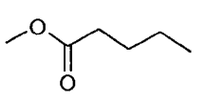
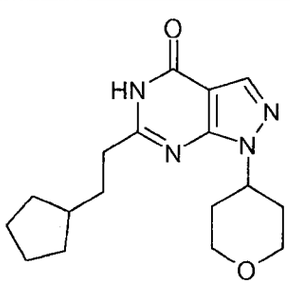
71. **SOLICITANTE** _____

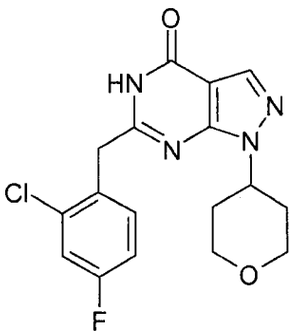
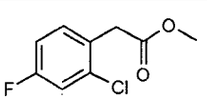
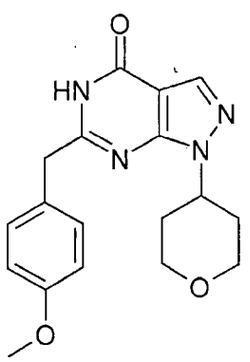
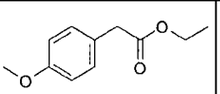
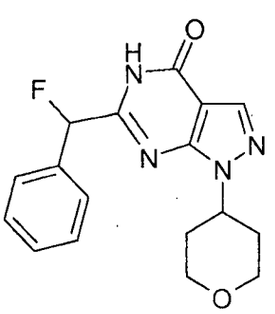
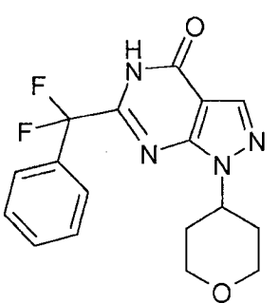
DOMICILIO _____

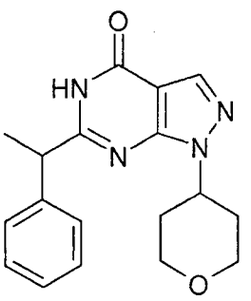
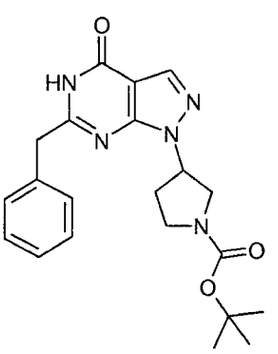
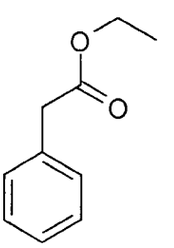
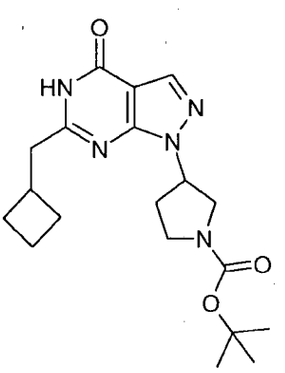
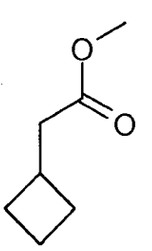
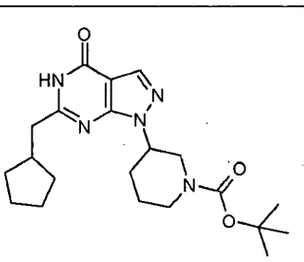
74. **APODERADO** _____

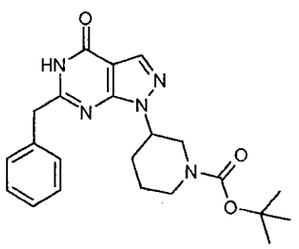
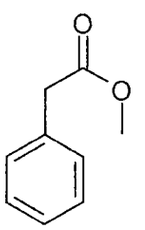
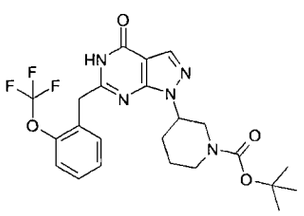
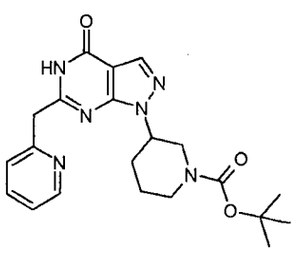
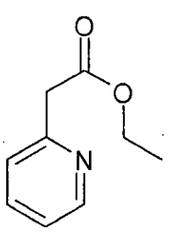
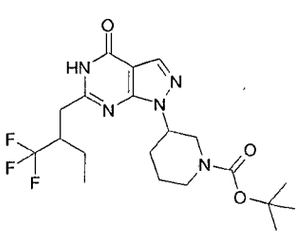
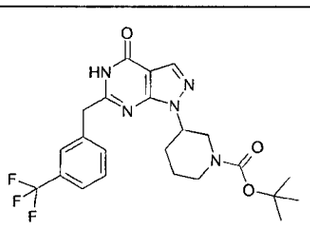
22. **BOGOTÁ, D.C.,** _____

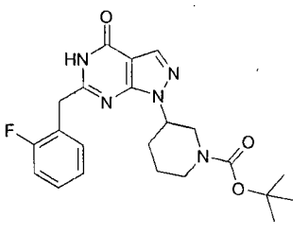
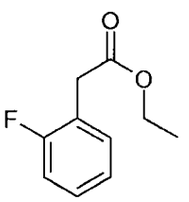
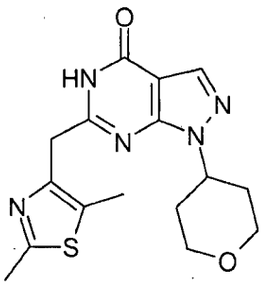
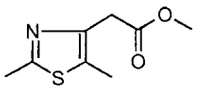
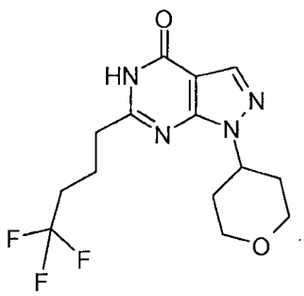
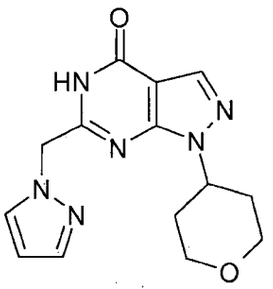
(FORMA P-10)

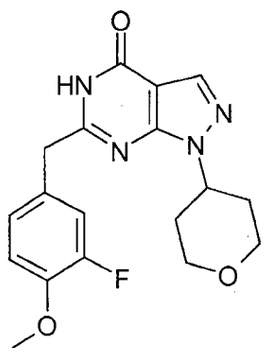
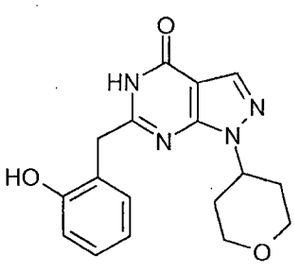
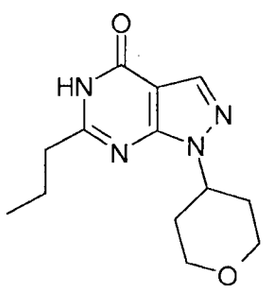
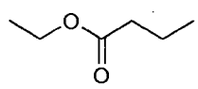
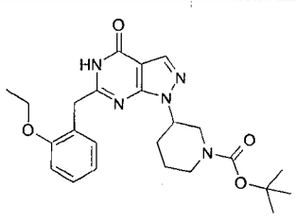
	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 6		Example 11B		1.28 (Method 1)	363/65 (Cl) $(M+H)^+$
Exp. 7		Example 11B	Example 5W	1.22 (Method 1)	345 $(M-H)^-$
Exp. 8		Exp. 11B		1.14 (Method 1)	277 $(M+H)^+$
Exp. 9		Exp. 11B	Example 5X	1.37 (Method 1)	317 $(M+H)^+$

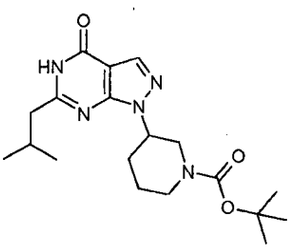
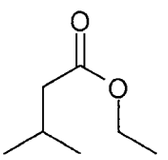
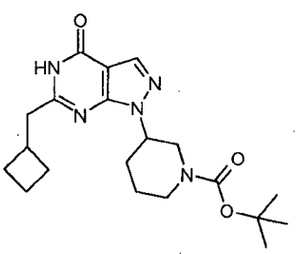
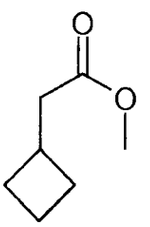
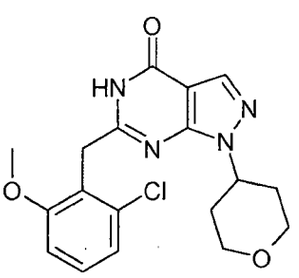
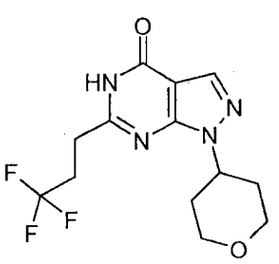
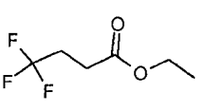
	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 10		Exp. 11B		1.30 (Method 1)	361/63 (Cl) $(M+H)^+$
Exp. 11		Exp. 11B		1.18 (Method 1)	341 $(M+H)^+$
Exp. 12 racem. mixture		Exp. 11B	Example 5AA	1.44 (Method 1)	329 $(M+H)^+$
Exp. 13		Exp. 11B	Example 5AB	1.26 (Method 1)	347 $(M+H)^+$

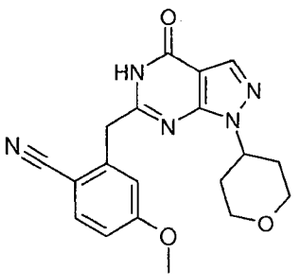
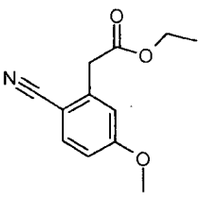
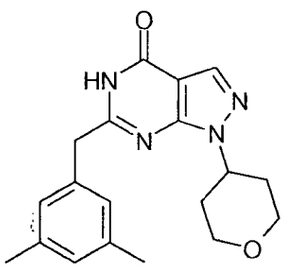
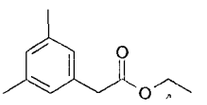
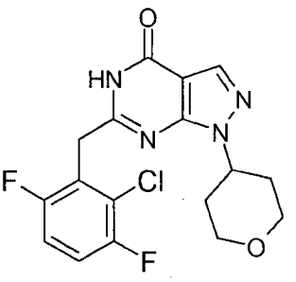
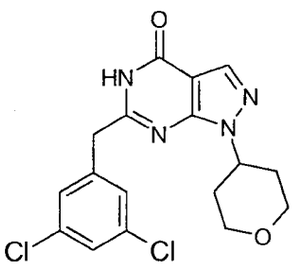
	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 14 racem. mixture		Exp. 11B	Example 5AF	1.28 (Method 1)	325 $(M+H)^+$
Exp. 15 racem. mixture		Exp. 11A		1.49 (Method1)	396 $(M+H)^+$
Exp. 16 racem. mixture		Exp. 11A		1.49 (Method 1)	374 $(M+H)^+$
Exp. 17 racem. mixture		Exp. 11D	Example 5AC	1.65 (Method 1)	402 $(M+H)^+$

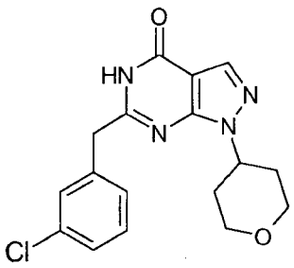
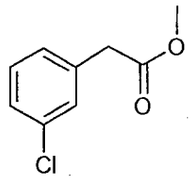
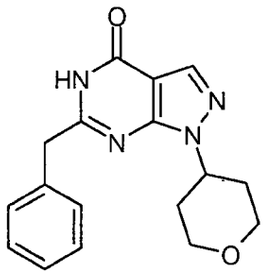
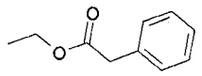
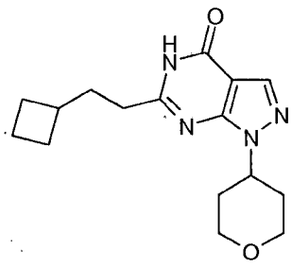
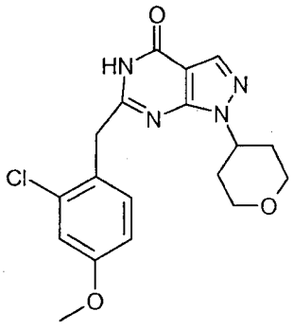
	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 18 racem. mixture		Exp. 11D		1.55 (Method 1)	408 $(M+H)^+$
Exp. 19 racem. mixture		Exp. 11D	Example 5AE	1.67 (Method1)	494 $(M+H)^+$
Exp. 20 racem. mixture		Exp. 11D		1.13 (Method 1)	411 $(M+H)^+$
Exp. 21 racem. mixture		Exp. 11D	Example 5T	1.63 (Method 1)	444 $(M+H)^+$
Exp. 22 racem. mixture		Exp. 11D	Example 5AH	1.66 (Method 1)	478 $(M+H)^+$

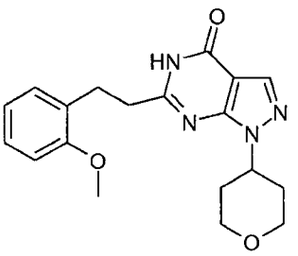
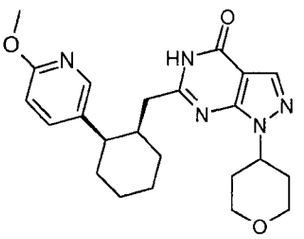
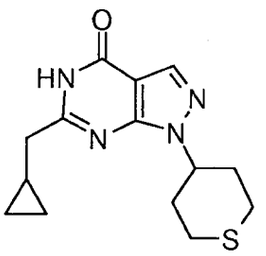
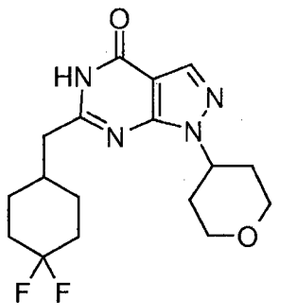
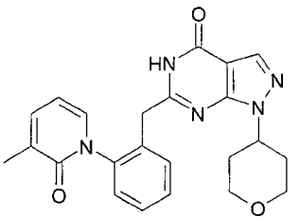
	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 23 racem. mixture		Exp. 11D		1.53 (Method 1)	428 $(M+H)^+$
Exp. 24		Exp. 11B		0.91 (Method 1)	346 $(M+H)^+$
Exp. 25		Exp. 11B	Example 5AI	1.17 (Method 1)	331 $(M+H)^+$
Exp. 26		Exp. 11B	Example 5AN	0.87 (Method 1)	301 $(M+H)^+$

	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 27		Exp. 11B	Example 5AJ	1.17 (Method 1)	359 $(M+H)^+$
Exp. 28		Exp. 11B	Example 5AM	1.08 (Method 1)	327 $(M+H)^+$
Exp. 29		Exp. 11B		1.02 (Method 1)	263 $(M+H)^+$
Exp. 30 racem. mixture		Exp. 11D	Example 5AK	1.63 (Method 1)	454 $(M+H)^+$

	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 31 racem. mixture		Exp. 11D		1.51 (Method 1)	376 $(M+H)^+$
Exp. 32 racem. mixture		Exp. 11D		1.56 (Method 1)	388 $(M+H)^+$
Exp. 33		Exp. 11B	Example 5AO	1.29 (Method 1)	375/377 (Cl) $(M+H)^+$
Exp. 34		Exp. 11B		1.11 (Method 1)	317 $(M+H)^+$

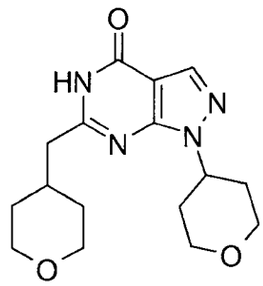
	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 35		Exp. 11B		1.17 (Method 1)	366 $(M+H)^+$
Exp. 36		Exp. 11B		1.36 (Method 1)	339 $(M+H)^+$
Exp. 37		Exp. 11B	Example 5AL	1.3 (Method 1)	381/383 (Cl) $(M+H)^+$
Exp. 38		Exp. 11B	Example 5Z	1.44 (Method 1)	379/381/383 (Cl_2) $(M+H)^+$

	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 39		Exp. 11B		1.28 (Method 1)	345/347 (Cl) $(M+H)^+$
Exp. 40		Exp. 11B		1.16 (Method 1)	311 $(M+H)^+$
Exp. 40-1		Exp. 11B	Exp. 5ALC	1.30 (Method 1)	303 $(M+H)^+$
Exp. 40-2		Exp. 11B	Example 5ALB	1.31 (Method 1)	375 $(M+H)^+$

	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)
Exp. 40-3		Exp. 11B	Example 5ALD	1.25 (Method 1)	355 $(M+H)^+$
Exp. 40-4 cis, racem. mixture		Exp. 11B	Exp. 5HA	1.18 (Method 1)	424 $(M+H)^+$
Exp. 40-5		Exp. 11IC	Exp. 5ALA	1.24 (Method 1)	291 $(M+H)^+$
Exp. 40-6		Exp. 11B	Example 5TA	1.22 (Method 1)	353 $(M+H)^+$
Exp. 40-7		Exp. 11B	Example 5AP	1.35 (Method 1)	418 $(M+H)^+$

	structure	starting material: pyrazole	starting material: ester	R_t [min]	MS (ESI pos/neg, m/z)

Example 41

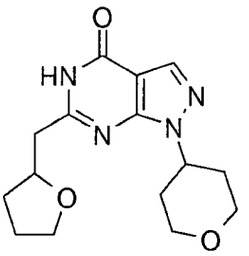
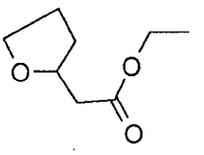
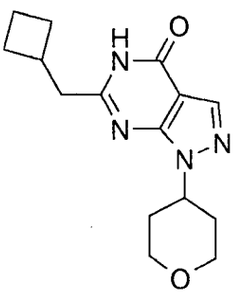
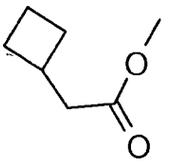
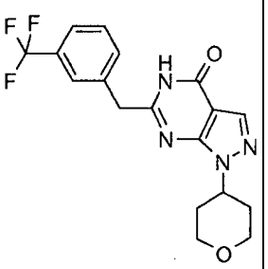
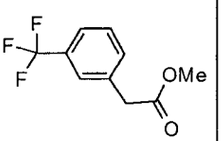
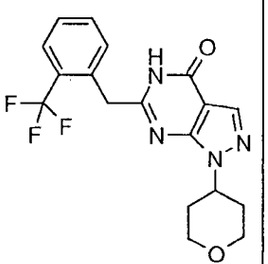
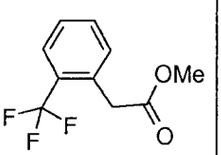


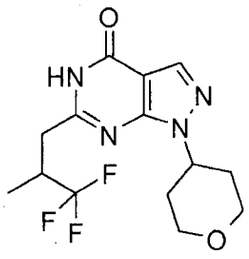
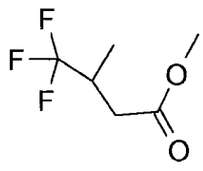
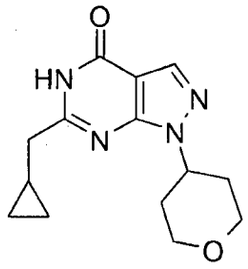
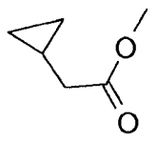
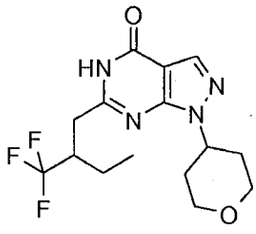
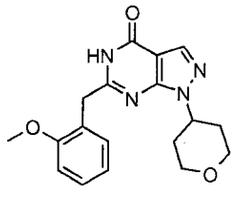
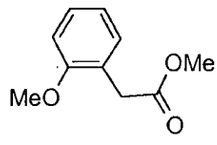
80 mg (0.38 mmol) of Example 11B were dissolved in 1 mL of absolute ethanol, 262 mg (1.52 mmol) of ethyl tetrahydropyran-4-yl-acetate, and 45.1 mg (1.10 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 40 min in a microwave oven. Cooling to 20°C was followed by evaporation of the solvent under reduced pressure. The residue was treated with water (10 mL), acidified with HCl (10 % in water) and extracted two times with dichloromethane (2 mL). The organic layer was dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure. The residue was triturated with ether to give 65 mg (53.7 %) of the product as a white solid.

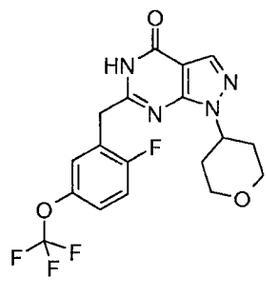
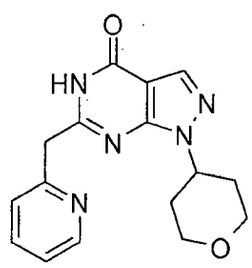
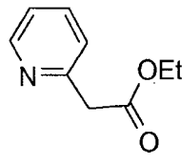
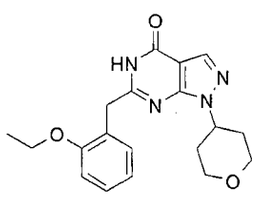
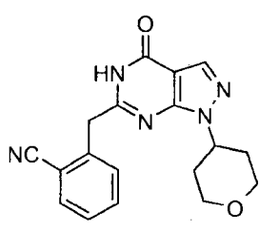
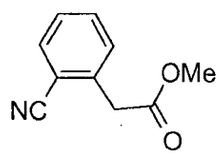
HPLC-MS (Method Grad_C8_NH_4COOH): R_t: 1.89 min

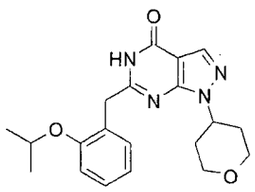
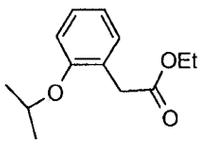
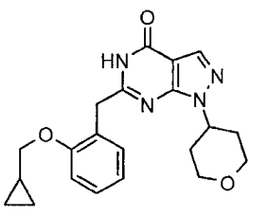
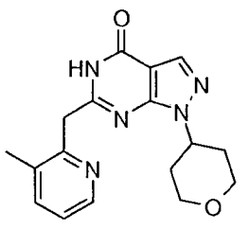
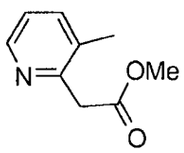
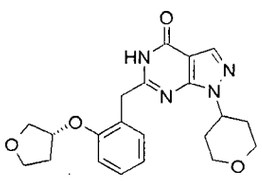
MS (ESI pos): m/z = 319 $(M+H)^+$.

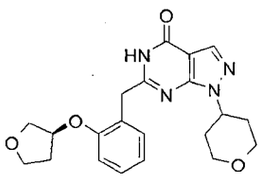
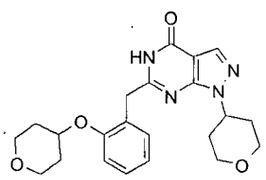
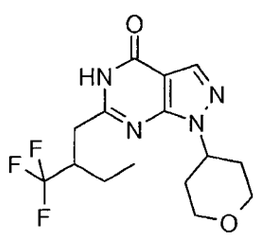
The following examples were synthesized in analogy to the preparation of Example 41, using the corresponding pyrazolyl-carboxamides and esters as starting materials.

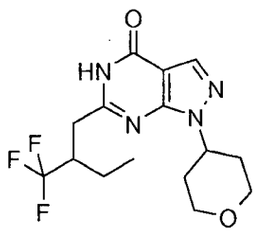
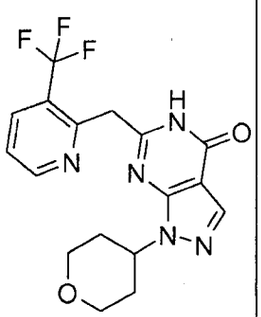
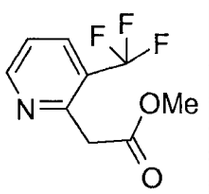
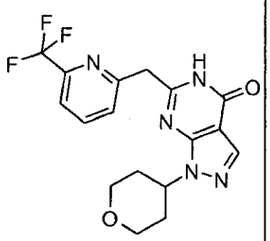
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 42 racem. mixture		Exp. 11B		2.02 (Method Grad_C8_ NH_4COOH)	305 $(M+H)^+$
Exp. 43		Exp. 11B		2.40 (Method Grad_C8_ NH_4COOH)	289 $(M+H)^+$
Exp. 44		Exp. 11B		3.06 (Method Grad_C8_ NH_4COOH)	379 $(M+H)^+$
Exp. 45		Exp. 11B		3.04 (Method Grad_C8_ NH_4COOH)	379 $(M+H)^+$

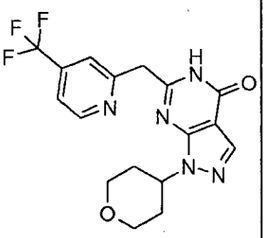
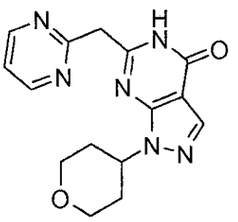
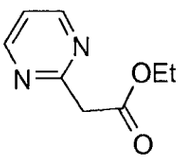
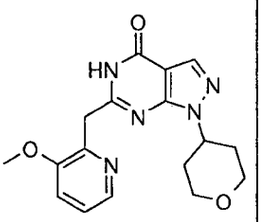
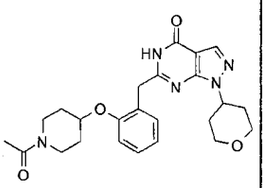
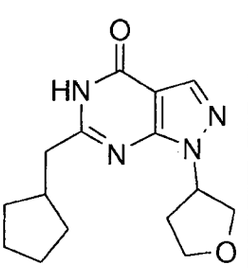
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 46 racem. mixture		Exp. 11B		2.77 (Method Grad_C8_ NH_4COOH)	331 $(M+H)^+$
Exp. 47		Exp. 11B		2.21 (Method Grad_C8_ NH_4COOH)	275 $(M+H)^+$
Exp. 48 racem. mixture		Exp. 11B	Exp. 5T	2.84 (Method Grad_C8_ NH_4COOH)	345 $(M+H)^+$
Exp. 49		Exp. 11B		2.57 (Method Grad_C8_ NH_4COOH)	341 $(M+H)^+$

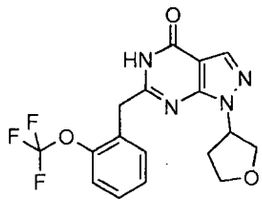
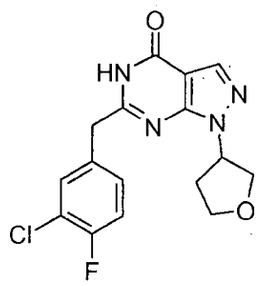
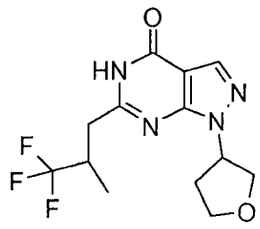
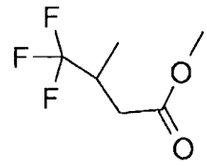
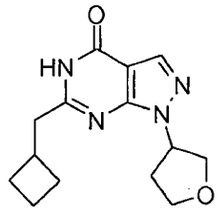
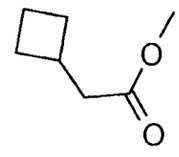
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 50		Exp. 11B	Exp. 5E	3.02 (Method Grad_C8_ NH_4COOH)	413 $(M+H)^+$
Exp. 51		Exp. 11B		5.97 (Method 1E hydro)	312 $(M+H)^+$
Exp. 52		Exp. 11B	Exp. 5AK	2.75 (Method Grad_C8_ NH_4COOH)	355 $(M+H)^+$
Exp. 53		Exp. 11B		2.75 (Method Grad_C8_ NH_4COOH)	336 $(M+H)^+$

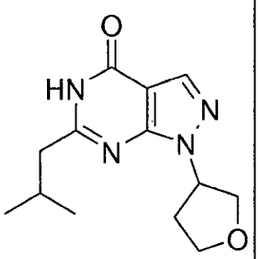
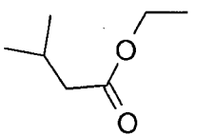
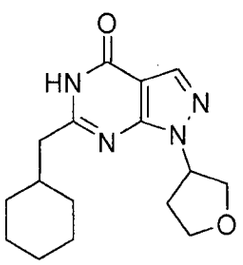
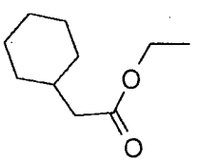
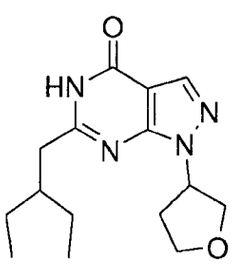
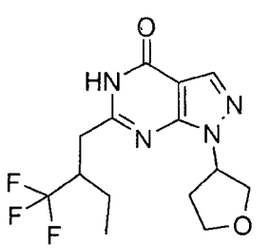
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 54		Exp. 11B		3.15 (Method Grad_C8_ NH_4COOH)	369 $(M+H)^+$
Exp. 55		Exp. 11B	Exp. 5K	3.21 (Method Grad_C8_ NH_4COOH)	381 $(M+H)^+$
Exp. 56		Exp. 11B		6.52 (Method 1E hydro)	326 $(M+H)^+$
Exp. 57 Enantio-mer R		Exp. 11B	Exp. 5M	2.64 (Method Grad_C8_ NH_4COOH)	397 $(M+H)^+$

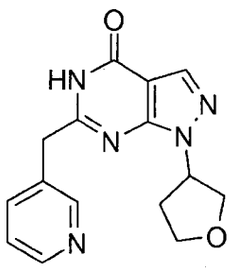
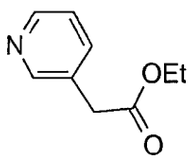
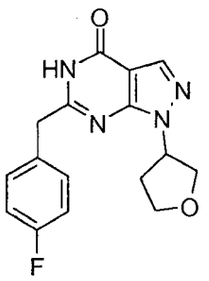
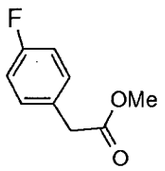
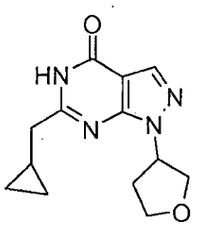
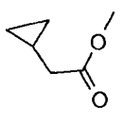
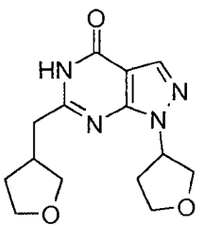
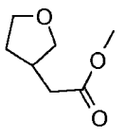
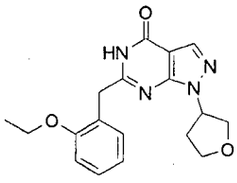
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 58 Enantio-mer S		Exp. 11B	Exp. 5L	2.64 (Method Grad_C8_ NH_4COOH)	397 $(M+H)^+$
Exp. 60		Exp. 11B	Exp. 5O	2.78 (Method Grad_C8_ NH_4COOH)	411 $(M+H)^+$
Exp. 61 Enantio-mer A		Exp. 11B	Exp. 5A	2.68 (Method Grad_C8_ NH_4COOH) 15.32 (Chiral 1)	345 $(M+H)^+$

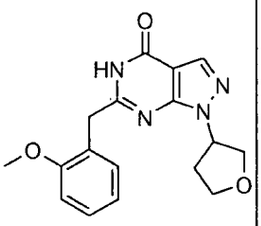
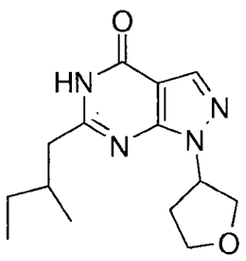
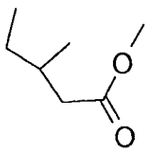
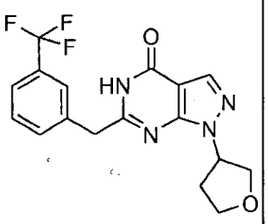
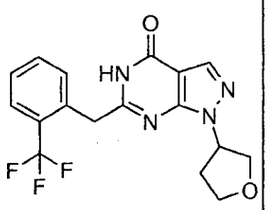
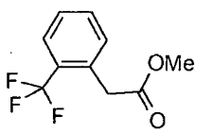
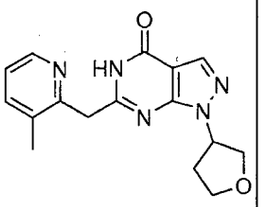
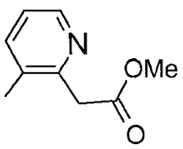
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 62 Enantio-mer B		Exp. 11B	Exp. 5D	2.68 (Method Grad_C8_ NH_4COOH) 18.74 (Chiral 1)	345 $(M+H)^+$
Exp. 63		Exp. 11B		9.37 (Method 2F)	380 $(M+H)^+$
Exp. 64		Exp. 11B	Exp. 5S	6.75 (Method 1E hydro)	380 $(M+H)^+$

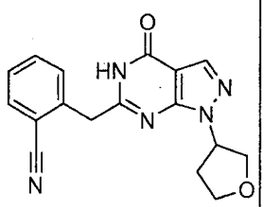
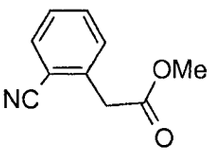
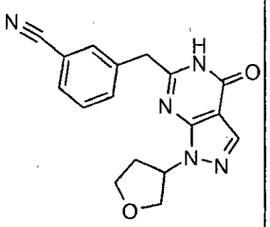
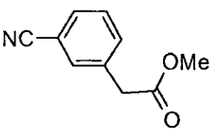
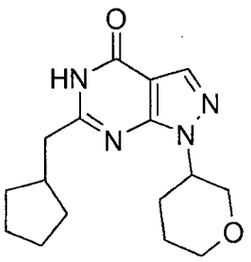
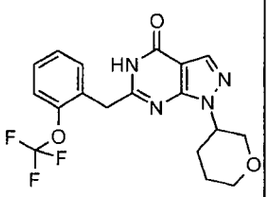
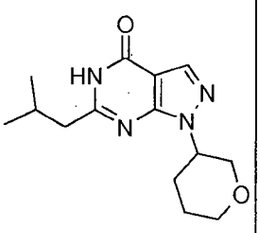
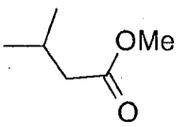
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 65		Exp. 11B	Exp. 5R	9.45 (Method 2F)	380 $(M+H)^+$
Exp. 66		Exp. 11B		6.70 (Method 2F)	313 $(M+H)^+$
Exp. 67		Exp. 11B	Exp. 5Q	2.38 (Method Grad_C8_ NH_4COOH)	342 $(M+H)^+$
Exp. 68		Exp. 11B	Exp. 5I	1.95 (Method Grad_C8_ NH_4COOH)	452 $(M+H)^+$
Exp. 69 racem. mixture		Exp. 11E	Exp. 5AC	7.30 (Method 1E)	289 $(M+H)^+$

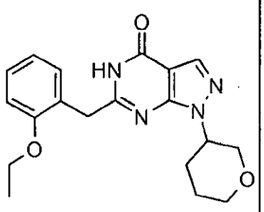
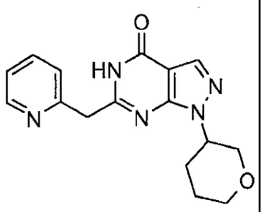
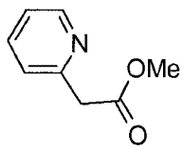
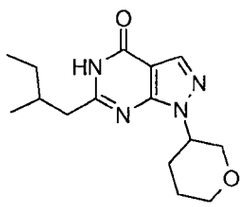
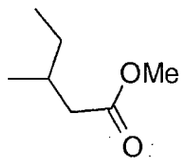
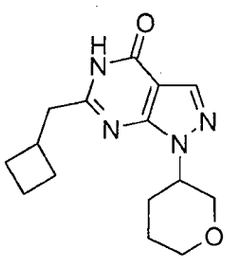
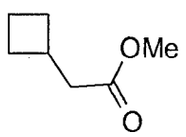
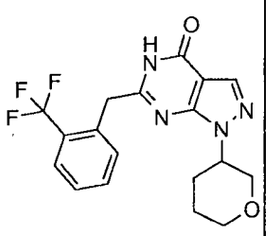
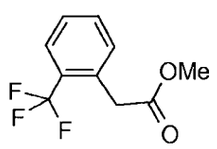
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 70 racem. mixture		Exp. 11E	Exp. 5AE	7.70 (Method 1E fusion)	381 $(M+H)^+$
Exp. 71 racem. mixture		Exp. 11E	Exp. 5F	7.68 (Method 1E fusion)	349 $(M+H)^+$
Exp. 72 mixture of stereoisomers		Exp. 11E		9.82 (Method 2F)	317 $(M+H)^+$
Exp. 73 racem. mixture		Exp. 11E		9.44 (Method 2F)	275 $(M+H)^+$

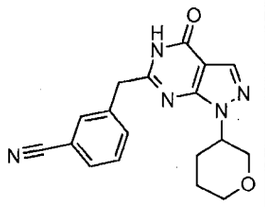
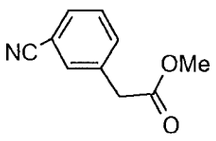
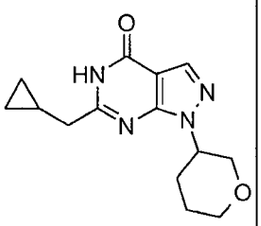
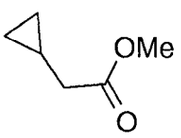
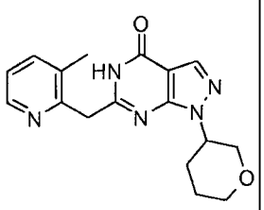
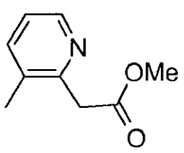
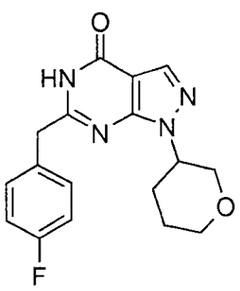
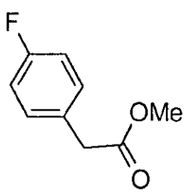
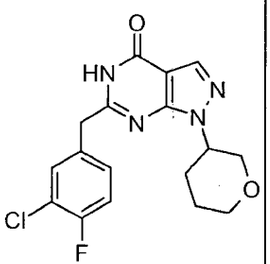
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 74 racem. mixture		Exp. 11E		8.89 (Method 2F)	263 $(M+H)^+$
Exp. 75 racem. mixture		Exp. 11E		10.69 (Method 2F)	303 $(M+H)^+$
Exp. 76 racem. mixture		Exp. 11E	Exp. 5H	10.57 (Method 2F)	291 $(M+H)^+$
Exp. 77 mixture of stereoisomers		Exp. 11E	Exp. 5T	10.55 (Method 2F)	331 $(M+H)^+$

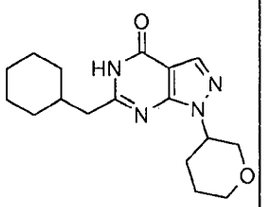
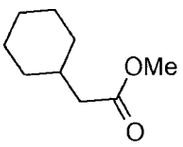
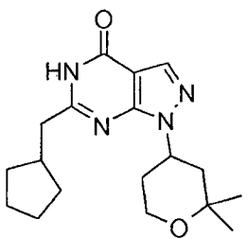
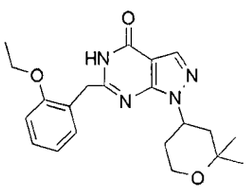
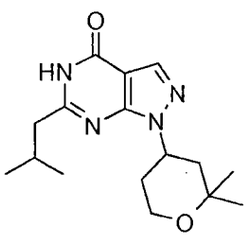
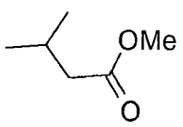
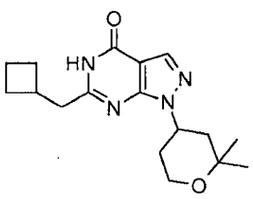
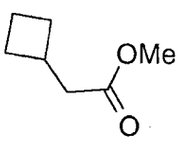
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 78 racem. mixture		Exp. 11E		4.83 (Method 1E Hydro)	298 $(M+H)^+$
Exp. 79 racem. mixture		Exp. 11E		7.10 (Method 1E fusion)	315 $(M+H)^+$
Exp. 80 racem. mixture		Exp. 11E		5.97 (Method 1E fusion)	261 $(M+H)^+$
Exp. 81 mixture of stereoisomers		Exp. 11E		4.73 (Method 1E hydro)	291 $(M+H)^+$
Exp. 82 racem. mixture		Exp. 11E	Exp. 5AK	7.37 (Method 1E hydro)	341 $(M+H)^+$

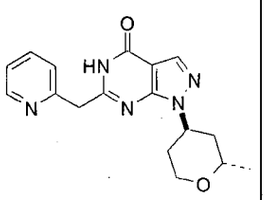
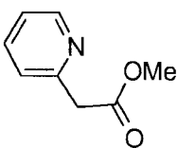
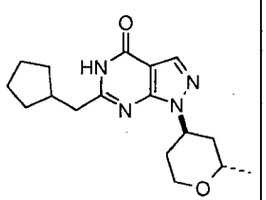
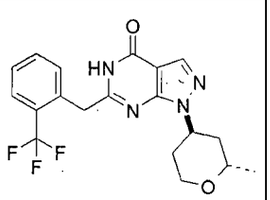
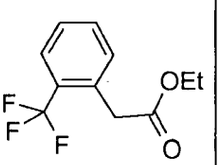
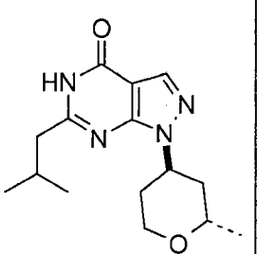
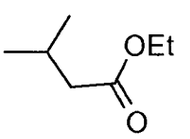
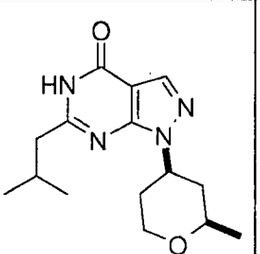
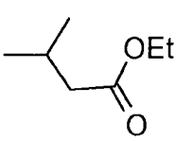
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 83 racem. mixture		Exp. 11E	Exp. 5AD	6.85 (Method 1E hydro)	327 $(M+H)^+$
Exp. 84 mixture of stereoisomers		Exp. 11E		6.88 (Method 1E hydro)	277 $(M+H)^+$
Exp. 85 racem. mixture		Exp. 11E	Exp. 5AH	7.93 (Method 1E hydro)	365 $(M+H)^+$
Exp. 86 racem. mixture		Exp. 11E		10.93 (Method 2F)	365 $(M+H)^+$
Exp. 87 racem. mixture		Exp. 11E		5.43 (Method 1E hydro)	312 $(M+H)^+$

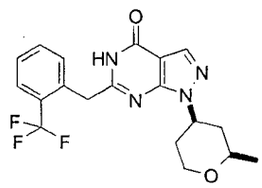
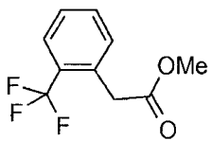
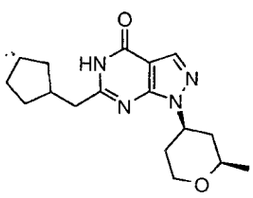
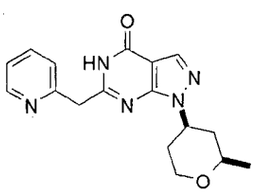
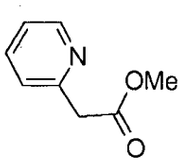
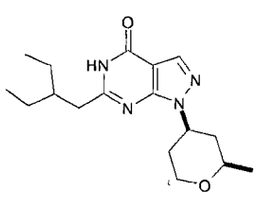
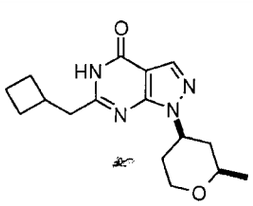
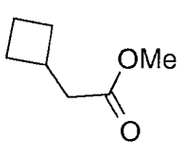
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 88 racem. mixture		Exp. 11E		5.43 (Method 1E hydro)	312 $(M+H)^+$
Exp. 89 racem. mixture		Example 11E		5.28 (Method 1E hydro)	322 $(M+H)^+$
Exp. 90 racem. mixture		Exp. 11F	Exp. 5AC	8 (Method 1E hydro)	303 $(M+H)^+$
Exp. 91 racem. mixture		Exp. 11F	Exp. 5AE	8.45 (Method 1E hydro)	395 $(M+H)^+$
Exp. 92 racem. mixture		Exp. 11F		6.93 (Method 1E hydro)	277 $(M+H)^+$

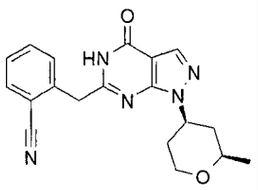
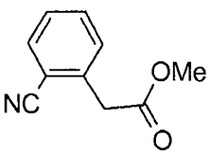
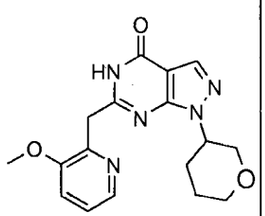
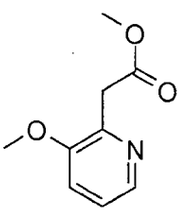
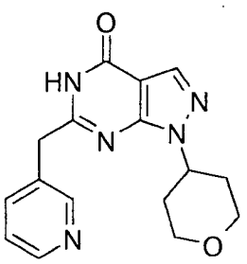
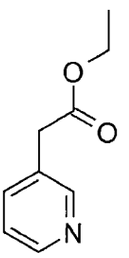
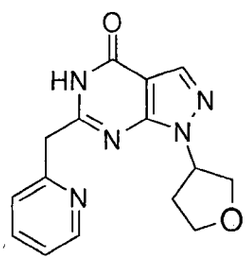
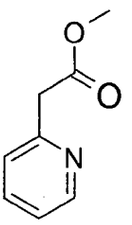
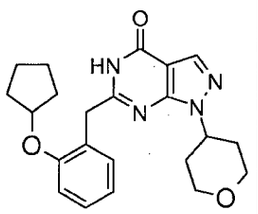
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 93 racem. mixture		Exp. 11F	Exp. 5AK	8.20 (Method 1E hydro)	355 $(M+H)^+$
Exp. 94 racem. mixture		Exp. 11F		6.28 (Method 1E hydro)	312 $(M+H)^+$
Exp. 95 mixture of stereoisomers		Exp. 11F		7.70 (Method 1E hydro)	291 $(M+H)^+$
Exp. 96 racem. mixture		Exp. 11F		7.33 (Method 1E hydro)	289 $(M+H)^+$
Exp. 97 racem. mixture		Exp. 11F		8.17 (Method 1E hydro)	379 $(M+H)^+$

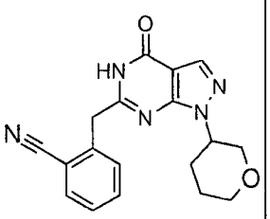
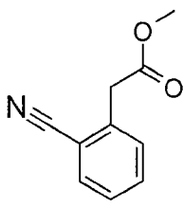
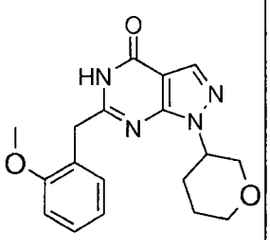
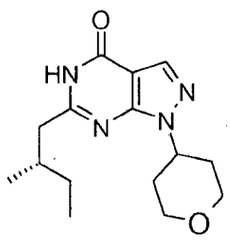
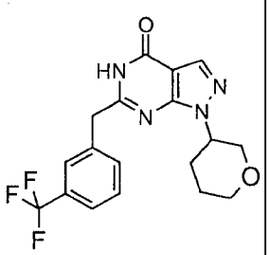
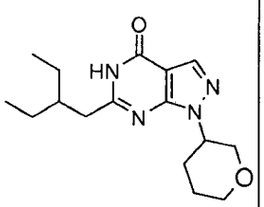
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 98 racem. mixture		Exp. 11F		6.80 (Method 1E hydro)	336 $(M+H)^+$
Exp. 99 racem. mixture		Exp. 11F		6.43 (Method 1E hydro)	275 $(M+H)^+$
Exp. 100 racem. mixture		Exp. 11F		2.38 (Method 2F)	326 $(M+H)^+$
Exp. 101 racem. mixture		Exp. 11F		7.52 (Method 1E hydro)	329 $(M+H)^+$
Exp. 102 racem. mixture		Exp. 11F	Exp. 5F	8.28 (1E hydro)	363 $(M+H)^+$

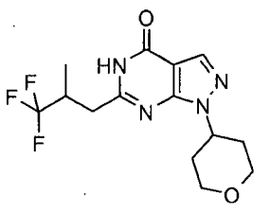
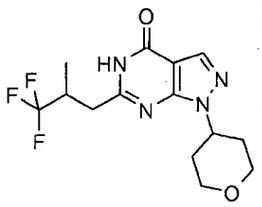
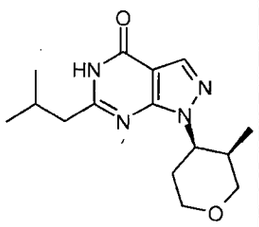
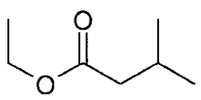
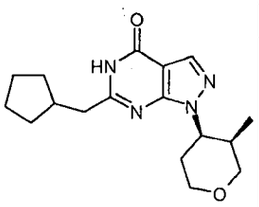
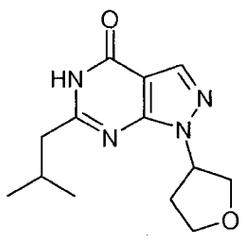
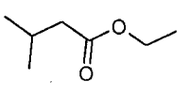
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 103 racem. mixture		Exp. 11F		8.70 (Method 1E hydro)	317 $(M+H)^+$
Exp. 104 racem. mixture		Exp. 11G	Exp. 5AC	8.57 (Method 1E hydro)	331 $(M+H)^+$
Exp. 105 racem. mixture		Exp. 11G	Exp. 5AK	8.62 (Method 1E hydro)	383 $(M+H)^+$
Exp. 106 racem. mixture		Exp. 11G	Methyliso-valerate 	7.58 (Method 1E hydro)	305 $(M+H)^+$
Exp. 108 racem. mixture		Exp. 11G	Cyclobutyl-acetic acid methyl ester 	7.93 (Method 1E)	317 $(M+H)^+$

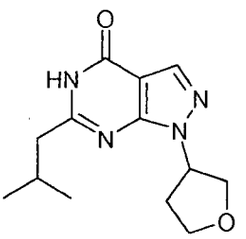
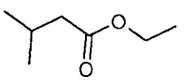
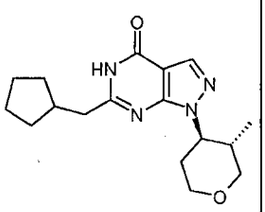
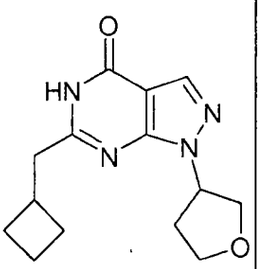
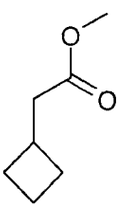
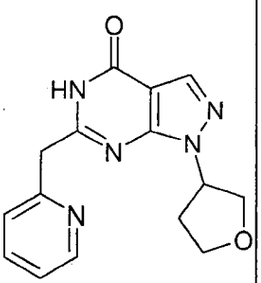
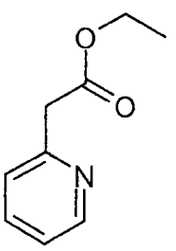
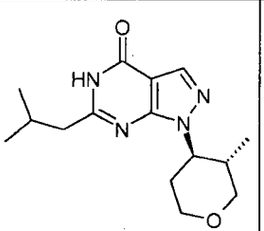
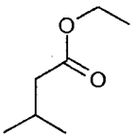
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 111 trans; racem. mixture		Exp. 11H		2.05 (Method 2F)	326 $(M+H)^+$
Exp. 112 trans; racem. mixture		Exp. 11H	Exp. 5AC	8.25 (Method 2F)	317 $(M+H)^+$
Exp. 113 trans; racem. mixture		Exp. 11H		8.42 (Method 1E hydro)	393 $(M+H)^+$
Exp. 114 trans; racem. mixture		Exp. 11H		7.15 (Method 1E hydro)	291 $(M+H)^+$
Exp. 115 cis; racem. mixture		Exp. 11I		9.90 (Method 2F)	291 $(M+H)^+$

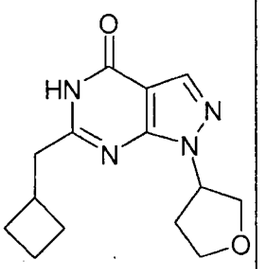
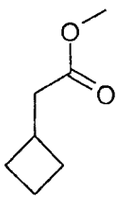
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 116 cis; racem. mixture		Exp. 11l		8.18 (Method 1E hydro)	393 $(M+H)^+$
Exp. 117 cis; racem. mixture		Exp. 11l	Exp. 5AC	7.98 (Method 1E hydro)	317 $(M+H)^+$
Exp. 118 cis; racem. mixture		Exp. 11l		5.80 (Method 1E hydro)	326 $(M+H)^+$
Exp. 119 cis; racem. mixture		Exp. 11l	Exp. 5H	8.42 (Method 1E hydro)	319 $(M+H)^+$
Exp. 120 cis; racem. mixture		Exp. 11l		7.33 (Method 1E hydro)	303 $(M+H)^+$

	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 121 cis; racem. mixture		Exp. 11I		9.91 (Method 2F)	350 $(M+H)^+$
Exp. 122 racem. mixture		Exp. 11F		6.95 (Method 2F)	342 (M+H)+
Exp. 123		Exp. 11B		2.12 (Method Grad_C8_ NH_4COOH)	312 $(M+H)^+$
Exp. 124 racem. mixture		Exp. 11E		4.98 (Method 1E hydro)	298 $(M+H)^+$
Exp. 125		Exp. 11B	Exp. 5P	8.72 (Method 1E hydro)	395 $(M+H)^+$

	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 126 racem. mixture		Exp. 11F		9.72 (Method 2F)	336 $(M+H)^+$
Exp. 127 racem. mixture		Exp. 11F	Exp. 5AB	7.62 (Method 1E hydro)	341 $(M+H)^+$
Exp. 128 Enantio-mer S		Exp. 11B	Exp. 5G	9.83 (Method 2F)	291 $(M+H)^+$
Exp. 129 racem. mixture		Exp. 11F	Exp. 5AF	11.56 (Method 2F)	379 $(M+H)^+$
Exp. 130 racem. mixture		Exp. 11F	Exp. 5H	8.38 (Method 1E hydro)	305 $(M+H)^+$

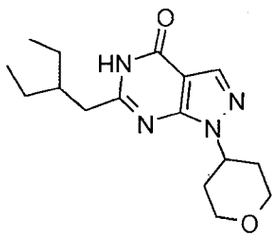
	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 131 Enantio-mer A		Exp. 11B	Exp. 5B	9.93 (Method 2F)	331 $(M+H)^+$
Exp. 132 Enantio-mer B		Exp. 11B	Exp. 5C	9.93 (Method 2F)	331 $(M+H)^+$
Exp. 132-1 cis, racem. mixture		Exp. 11IA		9.83 (Method 2F)	291 $(M+H)^+$
Exp. 132-2 cis, racem. mixture		Exp. 11IA	Exp. 5AC	10.96 (Method 2F)	317 $(M+H)^+$
Exp. 132-3 Enantio-mer A		Exp. 15A		8.84 (Method 2F)	263 $(M+H)^+$

	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 132-4 Enantio-mer B		Exp. 16A		8.96 (Method 2F)	263 $(M+H)^+$
Exp. 132-5 trans, racem. mixture		Exp. 11IB	Exp. 5AC	10.21 (Method 2F)	317 $(M+H)^+$
Exp. 132-6 Enantio-mer B		Exp. 16A		7.15 (Method 1E Hydro)	275 $(M+H)^+$
Exp. 132-7 Enantio-mer B		Exp. 16A		5.68 (Method 1E Hydro)	298 $(M+H)^+$
Exp. 132-8 trans, racem. mixture		Exp. 11IB		9.23 (Method 2F)	291 $(M+H)^+$

	Structure	pyrazolyl-carbox-amide	Ester	R_t [min]	MS (ESI, m/z)
Exp. 132-9 Enantio-mer A		Exp. 15A		8.83 (Method 2L)	275 $(M+H)^+$

Example 133

6-(2-Ethyl-butyl)-1-(tetrahydro-pyran-4-yl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one



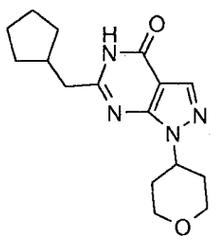
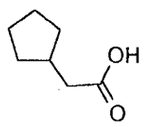
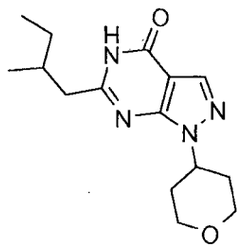
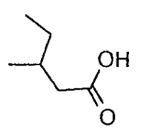
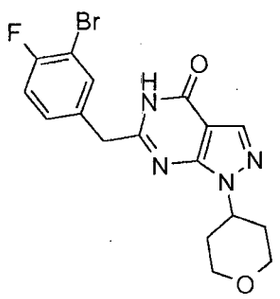
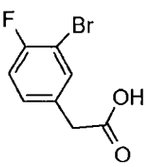
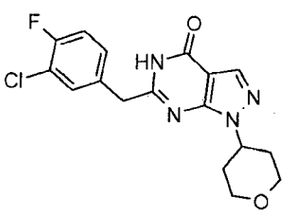
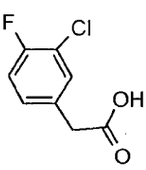
Example 11B (0.1 g, 0.48 mmol) was mixed with polyphosphoric acid (1.0 g) and 2-(trifluoromethoxy)phenylacetic acid (248 mg, 1.9 mmol) was added. The mixture was heated to 120°C during 16 hours. Temperature was lowered to 20°C and the pH value was adjusted to 7 by addition of ammonia (30 % solution in water). The aqueous phase was extracted with dichloromethane (2 x 20 mL) and the organic phase was dried over sodium sulphate. The crude mixture was purified by flash chromatography. Eluent: hexane/ethyl acetate 40/60.

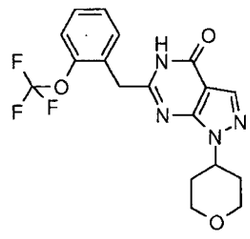
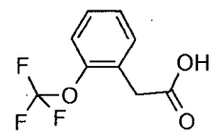
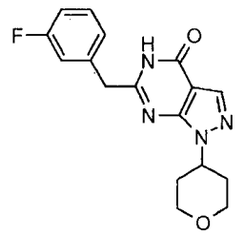
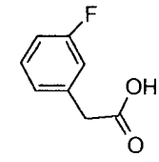
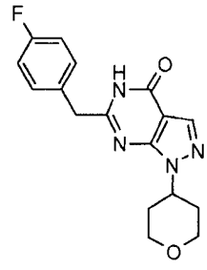
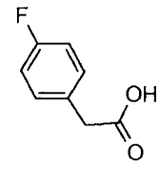
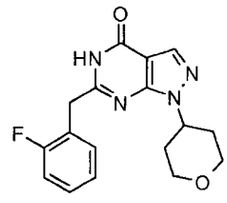
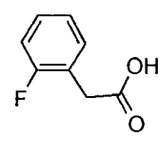
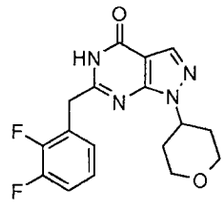
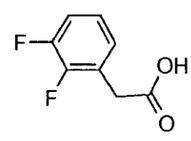
Obtained 23.5 mg (16 %) as a white solid

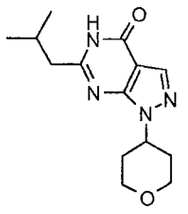
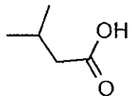
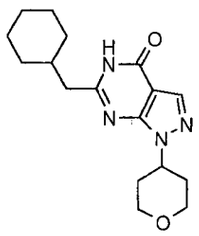
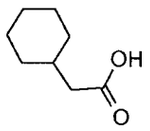
HPLC-MS (1E) R_t: 6.77 min

MS (APCI pos): m/z = 305 $(M+H)^+$

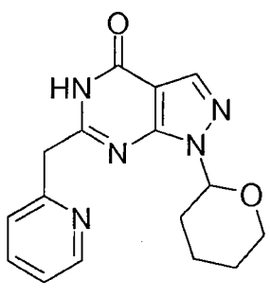
The following examples were synthesized in analogy to the preparation of Example 133, using the corresponding carboxylic acids as starting materials:

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 134			6.37 (Method 1E)	303 $(M+H)^+$
Example 135 racem. mixture			5.95 (Method 1E)	291 $(M+H)^+$
Example 136			6.57 (Method 1E)	407 $(M+H)^+$
Example 137			6.48 (Method 1E)	363 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 138			6.72 (Method 1E)	395 $(M+H)^+$
Example 139			2.71 (Method Grad_C8_NH_4COOH)	329 $(M+H)^+$
Example 140			2.77 (Method Grad_C8_NH_4COOH)	329 $(M+H)^+$
Example 141			2.90 (Method Grad_C8_NH_4COOH)	329 $(M+H)^+$
Example 142			3.07 (Method Grad_C8_NH_4COOH)	347 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 143			2.71 (Method Grad_C8_NH_4COOH)	277 $(M+H)^+$
Example 144			3.28 (Method Grad_C8_NH_4COOH)	317 $(M+H)^+$

Example 145, racemic mixture

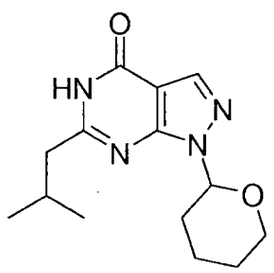
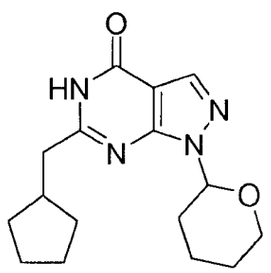
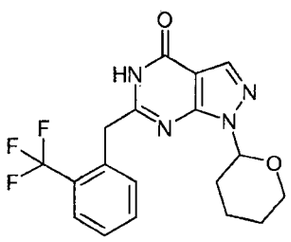


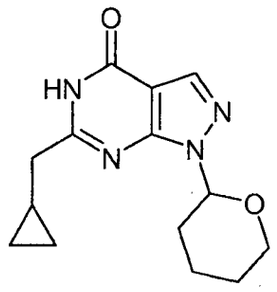
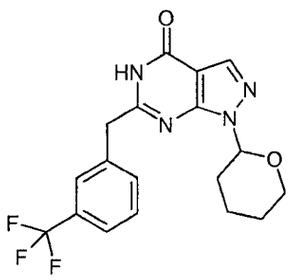
106 mg (0.47 mmol) Example 12V was mixed with 4 mL ethyl acetate and 0.5 mL dimethylformamide, 51 mg (0.61 mmol) 3.4-dihydro-2H-pyran and 88.4 mg (0.51 mmol) p-toluenesulfonic acid were added. The reaction mixture was heated to 60°C and stirred for 2h. After cooling to room temperature ethyl acetate was added and the mixture was washed with saturated sodium hydrogen carbonate and with saturated sodium chloride. The organic layer was evaporated under reduced pressure. The residue was purified by preparative HPLC-MS. 31.5 mg (21.7 %) were obtained.

MS (APCI pos): m/z = 312 $(M+H)^+$

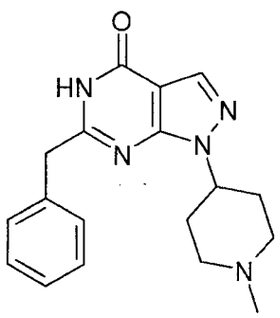
HPLC-MS (Method 2F) R_t: 8.26 min

The following examples were synthesized in analogy to the preparation of Example 145, using the corresponding pyrazolopyrimidinones as starting materials.

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 146 racem. mixture		Example 12W	9.99 (Method 2F)	277 $(M+H)^+$
Exp. 147 racem. mixture		Example 12X	10.98 (Method 2F)	303 $(M+H)^+$
Exp. 147-1 racem. mixture		Example 12Y	10.98 (Method 2F)	303 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 147-2 racem. mixture		Example 12AA	9.56 (Method 2F)	275 $(M+H)^+$
Example 147-3 racem. mixture		Example 12Z	11.62 (Method 2F)	379 $(M+H)^+$

Example 148

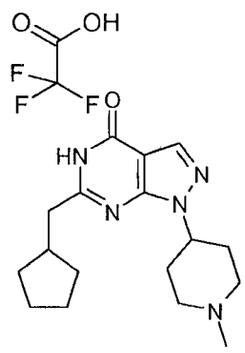
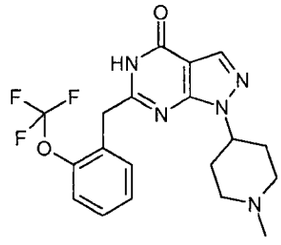


160 mg (470 mmol) of Example 12E was dissolved in 10 mL methanol and 350 mg Raney nickel was added. The reaction mixture was hydrogenated at room temperature for 6h, filtered and the solvent evaporated under reduced pressure. 100 mg (65 %) of the product were obtained.

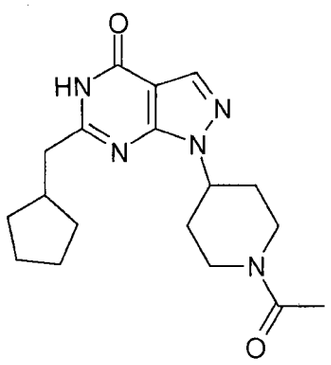
HPLC-MS (Method 1): R_t: 0.95 min

MS (ESI pos): m/z = 324 (M+H)

The following examples were synthesized in analogy to the preparation of Example 148, using the corresponding N-oxides as starting materials.

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 149		Example 12D	0.95 (Method 1)	316 $(M+H)^+$
Exp. 150		Example 12F	1.11 (Method 1)	408 $(M+H)^+$

Example 151



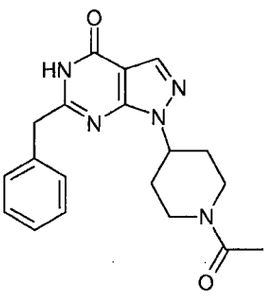
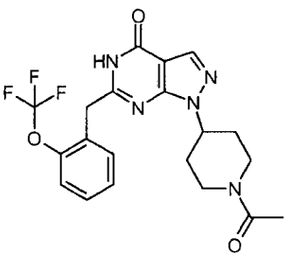
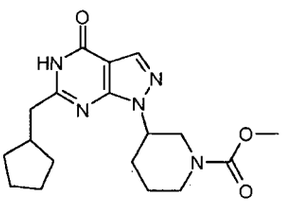
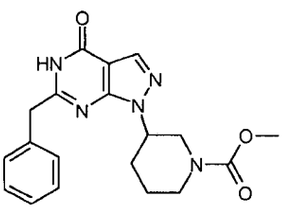
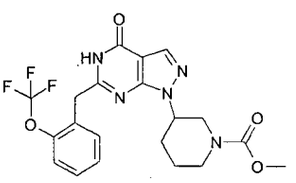
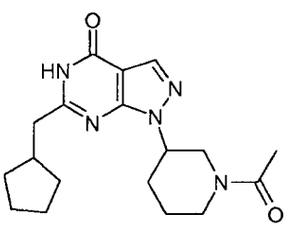
62 mg (150 mmol) of Example 13B were dissolved in 4 mL dichloromethane, 22.5 µL (300 mmol) acetyl chloride and 42 µL (300 mmol) triethylamine were added. The reaction mixture was stirred at room temperature over night. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 28 mg (55 %) of the product were obtained.

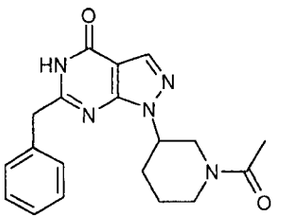
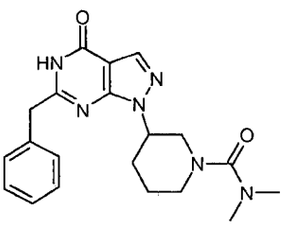
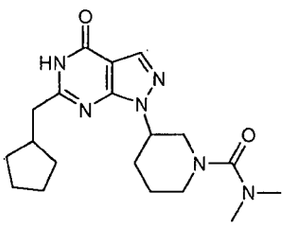
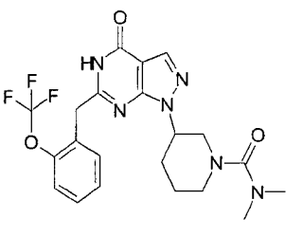
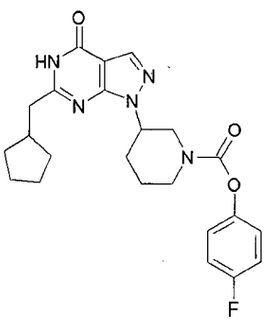
HPLC-MS (Method 1): R_t: 1.18 min

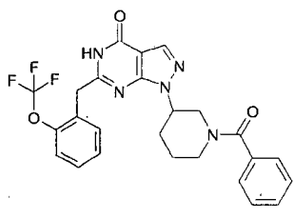
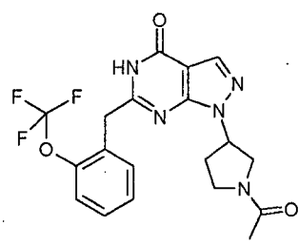
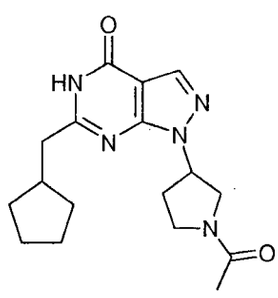
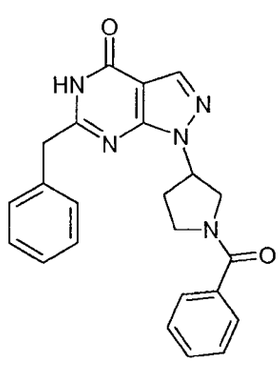
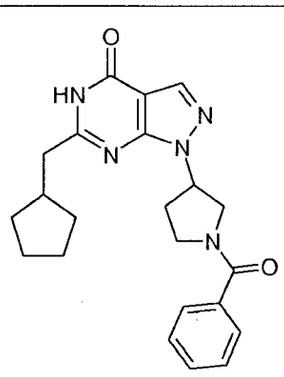
MS (ESI pos): m/z = 344 $(M+H)^+$

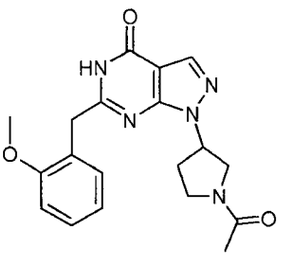
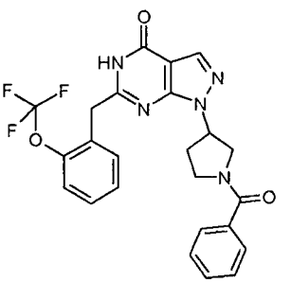
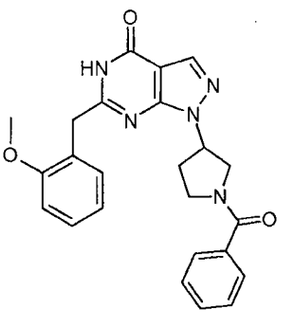
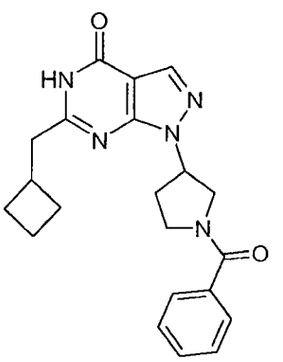
The following examples were synthesized in analogy to the preparation of Example 151, using the corresponding starting materials. It will be evident that as acylating agent not for all compounds acetylchloride has been introduced but other acylating agents like commercially available methoxychloroformate, substituted or unsubstituted aminocarbonylchloride, unsubstituted or substituted phenoxycarbonylchloride, unsubstituted or substituted benzoylchloride were used.

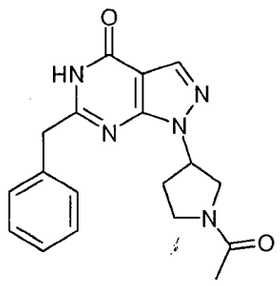
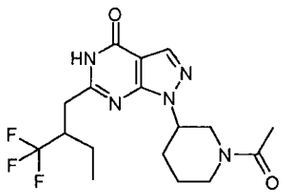
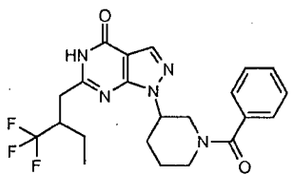
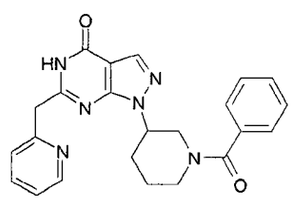
	structure	starting material	R_t [min]	MS (ESI, m/z)

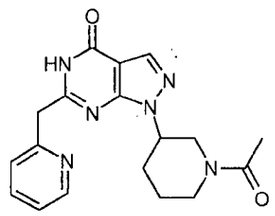
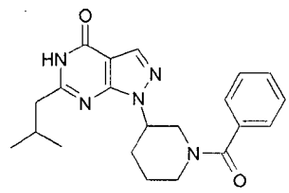
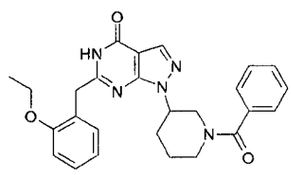
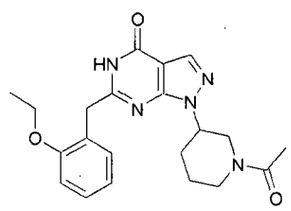
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 152		Example 13K	1.09 (Method 1)	352 $(M+H)^+$
Exp. 153		Example 13L	1.25 (Method 1)	436 $(M+H)^+$
Exp. 154 racem. mixture		Example 13C	1.38 (Method 1)	360 $(M+H)^+$
Exp. 155 racem. mixture		Example 13D	1.30 (Method 1)	368 $(M+H)^+$
Exp. 156 racem. mixture		Example 13E	1.44 (Method 1)	452 $(M+H)^+$
Exp. 157 racem. mixture		Example 13C	1.20 (Method 1)	344 $(M+H)^+$

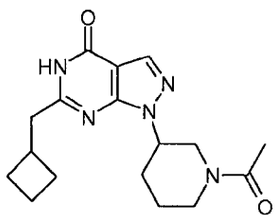
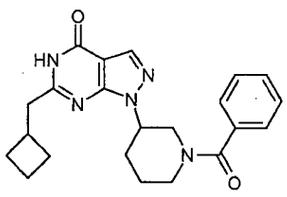
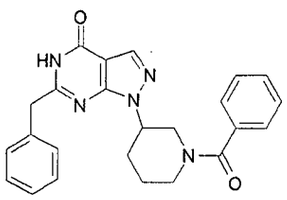
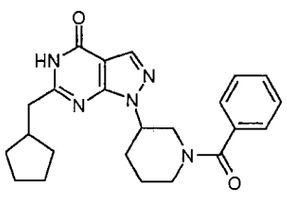
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 158 racem. mixture		Example 13D	1.16 (Method 1)	352 $(M+H)^+$
Exp. 159 racem. mixture		Example 13D	1.25 (Method 1)	381 $(M+H)^+$
Exp. 160 racem. mixture		Example 13C	1.30 (Method 1)	373 $(M+H)^+$
Exp. 161 racem. mixture		Example 13E	1.38 (Method 1)	465 $(M+H)^+$
Exp. 162 racem. mixture		Example 13C	1.62 (Method 1)	440 $(M+H)^+$

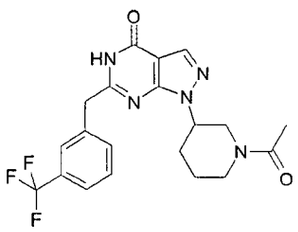
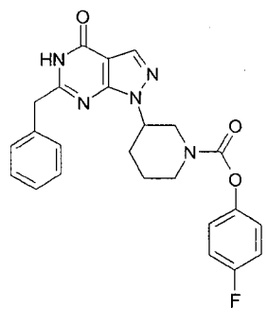
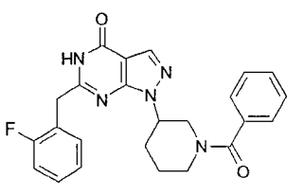
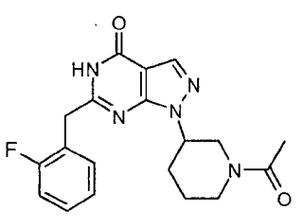
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 163 racem. mixture		Example 13E	1.48 (Method 1)	498 $(M+H)^+$
Exp. 164 racem. mixture		Example 13G	1.23 (Method1)	422 $(M+H)^+$
Exp. 165 racem. mixture		Example 13A	1.14 (Method1)	330 $(M+H)^+$
Exp. 166 racem. mixture		Example 13F	1.28 (Method1)	400 $(M+H)^+$
Exp. 167 racem. mixture		Example 13A	1.36 (Method1)	392 $(M+H)^+$

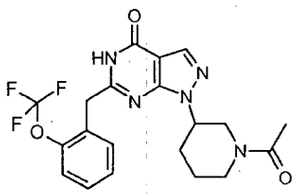
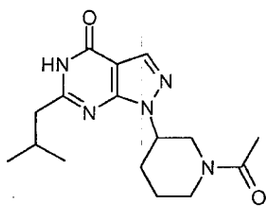
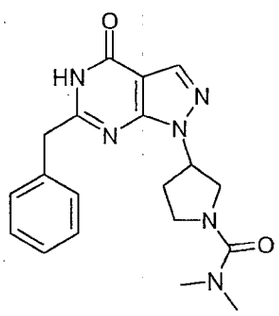
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 168 racem. mixture		Example 13H	1.1 (Method 1)	368 $(M+H)^+$
Exp. 169 racem. mixture		Example 13G	1.44 (Method 1)	484 $(M+H)^+$
Exp. 170 racem. mixture		Example 13H	1.32 (Method 1)	430 $(M+H)^+$
Exp. 171 racem. mixture		Example 13I	1.29 (Method 1)	378 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 172 racem. mixture		Example 13F	1.07 (Method 1)	338 $(M+H)^+$
Exp. 173 mixture of stereoisomers		Example 13M	1.25 (Method 1)	386 $(M+H)^+$
Exp. 174 mixture of stereoisomers		Example 13M	1.44 (Method 1)	448 $(M+H)^+$
Exp. 175 racem. mixture		Example 13N	1.04 (Method 1)	415 $(M+H)^+$

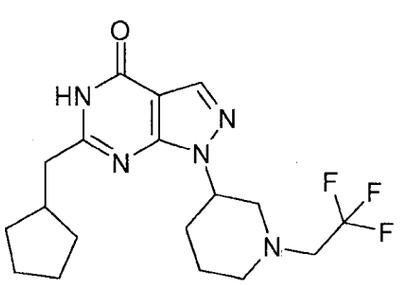
	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 176 racem. mixture		Example 13N	0.84 (Method 1)	353 $(M+H)^+$
Exp. 177 racem. mixture		Example 13O	1.31 (Method 1)	380 $(M+H)^+$
Exp. 178 racem. mixture		Example 13P	1.43 (Method 1)	458 $(M+H)^+$
Exp. 179 racem. mixture		Example 13P	1.24 (Method 1)	396 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 180 racem. mixture		Example 13Q	1.14 (Method 1)	330 $(M+H)^+$
Exp. 181 racem. mixture		Example 13Q	1.34 (Method 1)	392 $(M+H)^+$
Exp. 182 racem. mixture		Example 13D	1.35 (Method 1)	414 $(M+H)^+$
Exp. 183 racem. mixture		Example 13C	1.41 (Method 1)	406 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 184 racem. mixture		Example 205	1.30 (Method 1)	420 $(M+H)^+$
Exp. 185 racem. mixture		Example 13D	1.53 (Method 1)	448 $(M+H)^+$
Exp. 186 racem. mixture		Example 204	1.35 (Method 1)	432 $(M+H)^+$
Exp. 187 racem. mixture		Example 204	1.15 (Method 1)	370 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 188 racem. mixture		Example 13E	1.29 (Method 1)	436 $(M+H)^+$
Exp. 189 racem. mixture		Example 13O	1.08 (Method 1)	318 $(M+H)^+$
Exp. 190 racem. mixture		Example 13F	1.18 (Method 1)	367 $(M+H)^+$

Example 191, racemic mixture

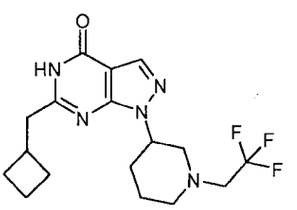
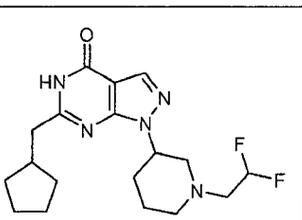


60 mg (0.2 mmol) of Example 13C were dissolved in 5 mL xylene and 57 mg (0.2 mmol) 2,2,2-trifluoroethyl-trichloromethansulfonate were added drop wise. The reaction mixture was heated to 140°C and stirred for 5h. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 24.8 mg (32 %) of the product were obtained.

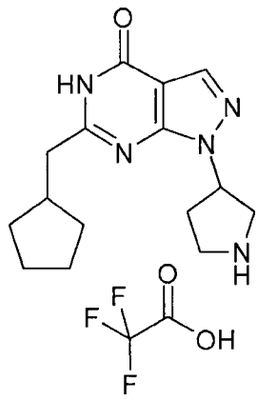
HPLC-MS (Method 1): R_t: 1.45 min

MS (ESI pos): m/z = 384 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 191, using the corresponding starting materials.

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 192 racem. mixture		Example 13Q	1.35 (Method 1)	370 $(M+H)^+$
Exp. 193 racem. mixture		Example 13C	1.07 (Method 1)	366 $(M+H)^+$

Example 194, racemic mixture

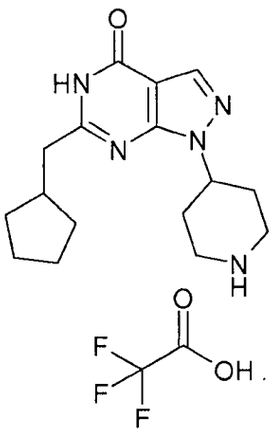


400 mg (1.35 mmol) of Example 11A were dissolved in 8 mL of absolute ethanol, 840 mg (5.4 mmol) of Example 5AC, and 220 mg (5.5 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. After cooling to room temperature, the reaction mixture was acidified with 4N hydrochloride acid. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 250 mg (46 %) of the product were obtained as a white solid.

HPLC-MS (Method 1): R_t: 0.93 min

MS (ESI pos): m/z = 288 $(M+H)^+$

Example 195



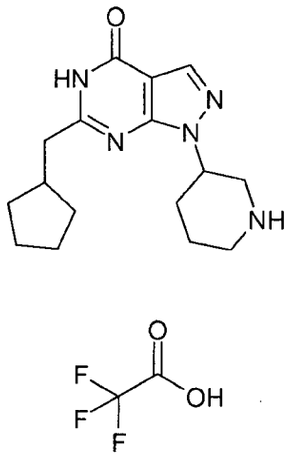
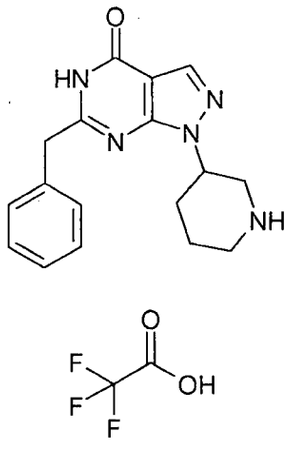
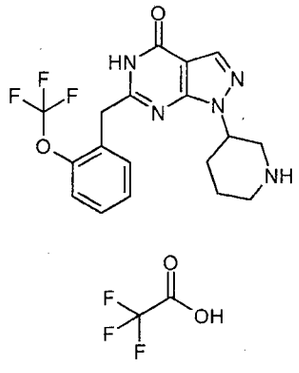
330 mg (0.82 mmol) of Example 12A were dissolved in 3 mL dichloromethane and 1 mL trifluoroacetic acid was added. The reaction mixture was stirred at room temperature over night. The solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 240 mg (70 %) of the product were obtained.

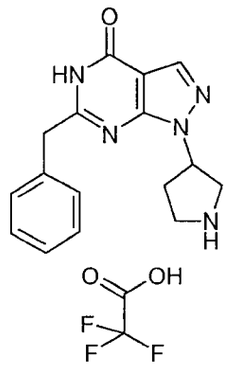
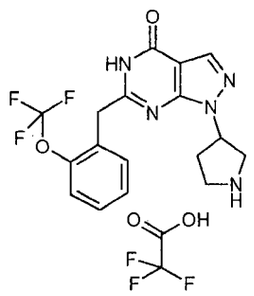
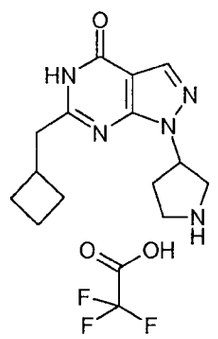
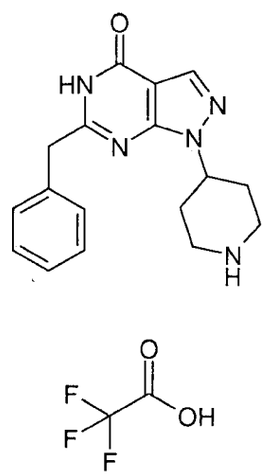
HPLC-MS (Method 1): R_t: 0.96 min

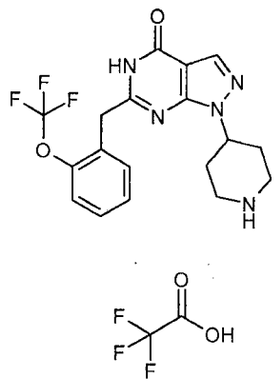
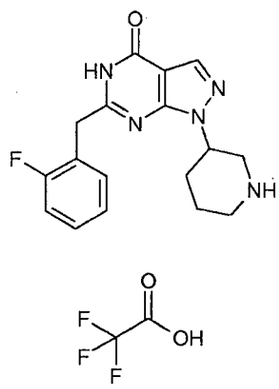
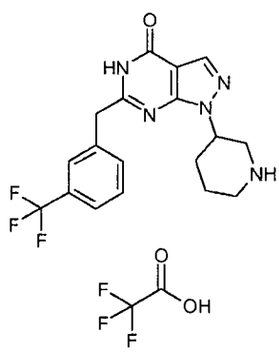
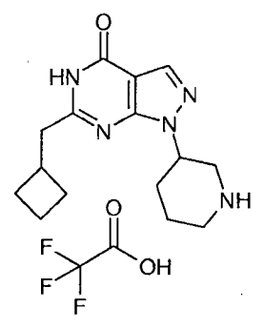
MS (ESI pos): m/z = 302 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 195, using the corresponding Boc-protected amines as starting materials.

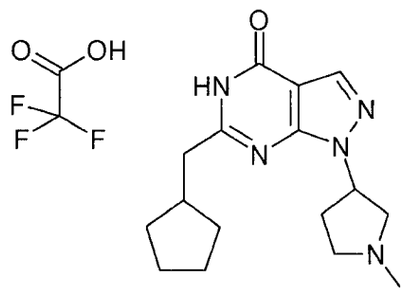
	structure	starting material	R_t [min]	MS (ESI, m/z)

Exp. 196 racem. mixture		Example 12L	1.01 (Method 1)	302 $(M+H)^+$
Exp. 197 racem. mixture		Example 12M	0.93 (Method 1)	310 $(M+H)^+$
Exp. 198 racem. mixture		Example 12N	1.09 (Method 1)	394 $(M+H)^+$

Exp. 199 racem. mixture		Example 12G	0.92 (Method 1)	296 $(M+H)^+$
Exp. 200 racem. mixture		Example 12H	1.08 (Method 1)	380 $(M+H)^+$
Exp. 201 racem. mixture		Example 12J	0.89 (Method 1)	274 $(M+H)^+$
Exp. 202		Example 12B	0.92 (Method1)	310 $(M+H)^+$

Exp. 203		Example 12C	1.07 (Method1)	394 $(M+H)^+$
Exp. 204 racem. mixture		Example 12Q	0.95 (Method 1)	328 $(M+H)^+$
Exp. 205 racem. mixture		Example 12R	1.13 (Method 1)	378 $(M+H)^+$
Exp. 206 racem. mixture		Example 12U	0.94 (Method 1)	288 $(M+H)^+$

Example 207, racemic mixture



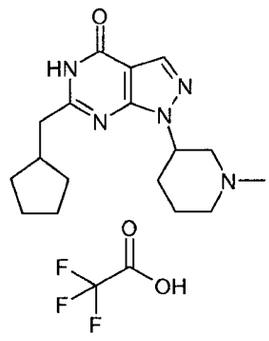
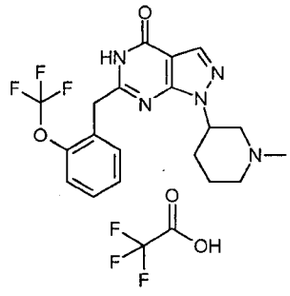
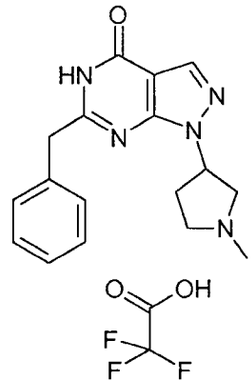
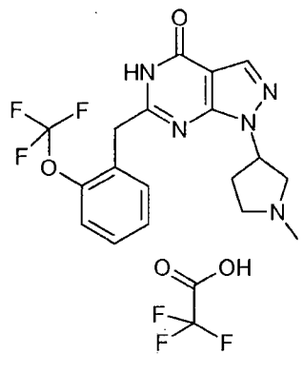
50 mg (120 mmol) of Example 13A were dissolved in 5 mL dichloromethane and 15 mg (500 mmol) of formaldehyde were added. The reaction mixture was stirred at room temperature for 1h. 15 µL (260 mmol) acetic acid and 35 mg (160 mmol) sodiumtriacetoxyborohydride were added. The reaction mixture was stirred 2h at room temperature. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 34 mg (65 %) of the product were obtained.

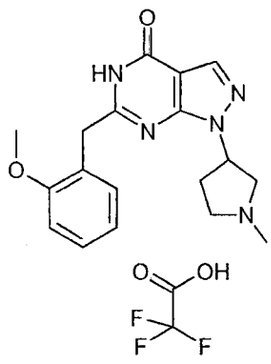
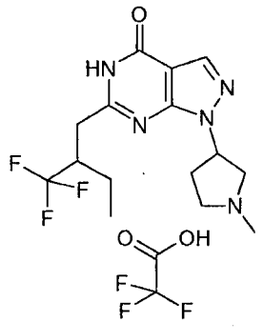
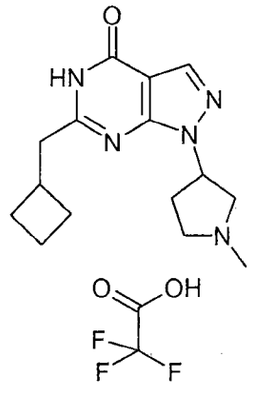
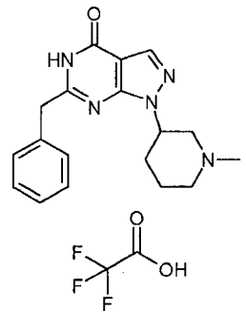
HPLC-MS (Method 1): R_t: 0.99 min

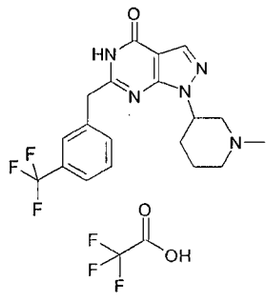
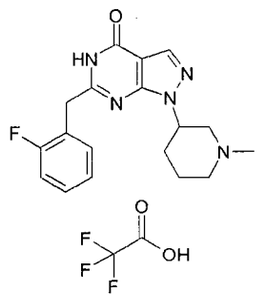
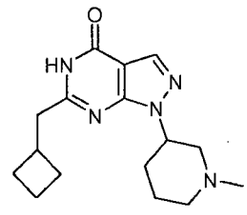
MS (ESI pos): m/z = 302 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 207 using the corresponding amines as starting materials

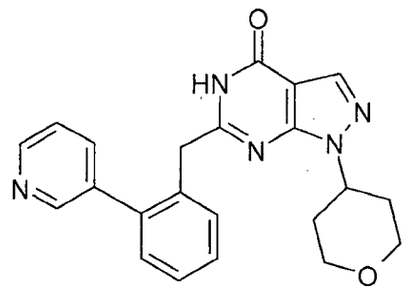
	structure	starting material	R_t [min]	MS (ESI, m/z)

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 208 racem. mixture		Example 13C	1.02 (Method 1)	316 $(M+H)^+$
Exp. 209 racem. mixture		Example 13E	1.13 (Method 1)	408 $(M+H)^+$
Exp. 210 racem. mixture		Example 13F	0.93 (Method 1)	310 $(M+H)^+$
Exp. 211 racem. mixture		Example 13G	1.11 (Method 1)	394 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 212 racem. mixture		Example 13H	0.98 (Method 1)	340 $(M+H)^+$
Exp. 213 mixture of stereoisomers		Example 13J	1.02 (Method 1)	344 $(M+H)^+$
Exp. 214 racem. mixture		Example 13I	0.91 (Method 1)	288 $(M+H)^+$
Exp. 215 racem. mixture		Example 13D	0.97 (Method 1)	324 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Exp. 216 racem. mixture		Example 205	1.16 (Method 1)	392 $(M+H)^+$
Exp. 217 racem. mixture		Example 204	0.98 (Method 1)	342 $(M+H)^+$
Exp. 218 racem. mixture		Example 13Q	0.95 (Method 1)	302 $(M+H)^+$

Example 219



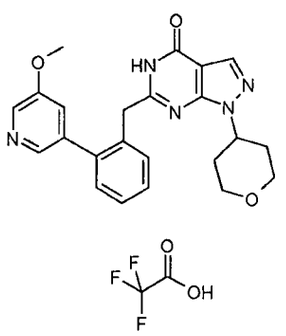
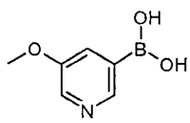
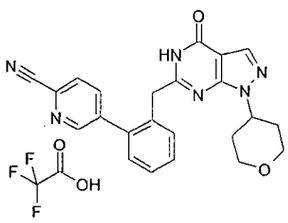
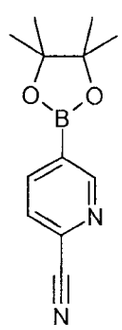
Under a argon atmosphere 100 mg (0.26 mmol) of example 5. 95 mg (0.77 mmol) pyridine-3-boronic acid, 310 µL (2.41 mmol) aqueous sodium carbonate solution (2 M), 5 mL dioxane and 20 mg (0.02 mmol) tetrakis-(triphenylphosohine)palladium(0)

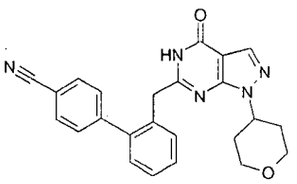
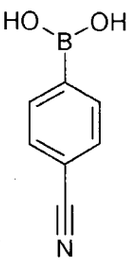
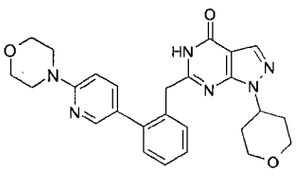
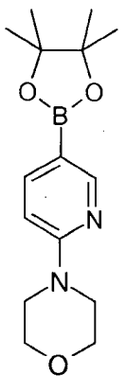
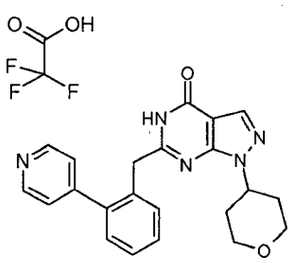
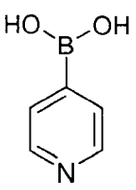
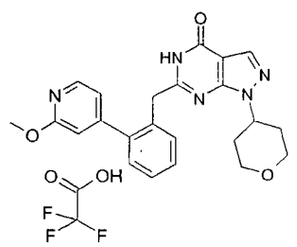
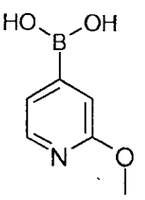
were combined. The reaction mixture was heated to 140°C for 35 min in a microwave oven. After cooling to room temperature the reaction mixture was filtered over celite. The filtrate was evaporated under reduced pressure. The residue was purified by preparative HPLC. 82 mg (83 %) of the product were obtained.

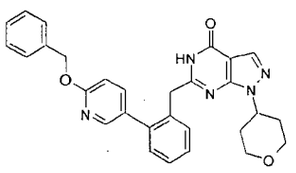
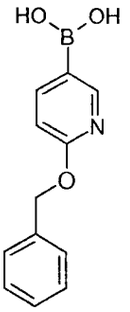
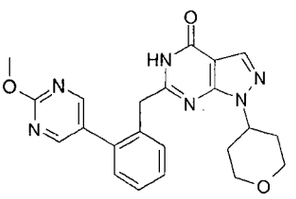
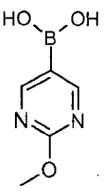
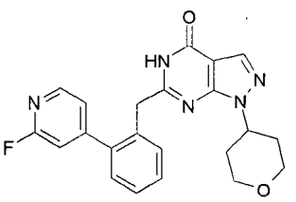
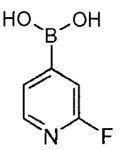
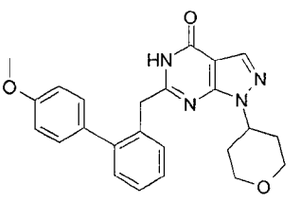
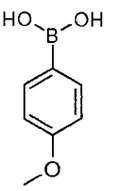
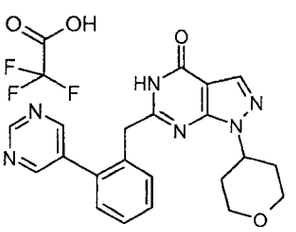
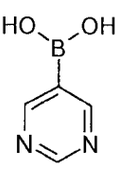
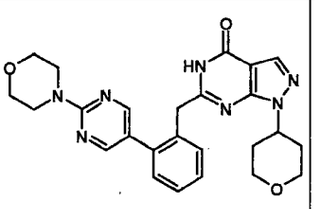
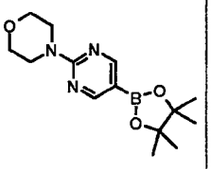
HPLC-MS (Method 1): R_t: 1.00 min

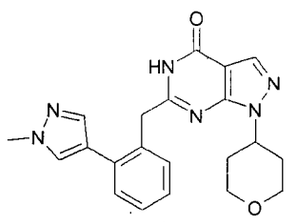
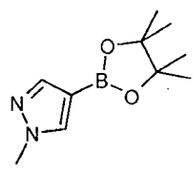
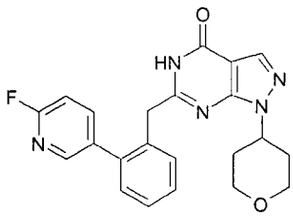
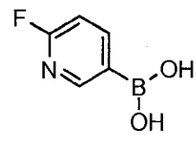
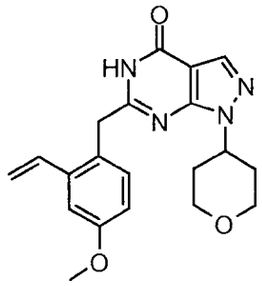
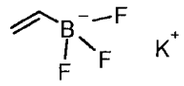
MS (ESI pos): m/z = 388 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of example 219 using the corresponding boronic acids as starting materials.

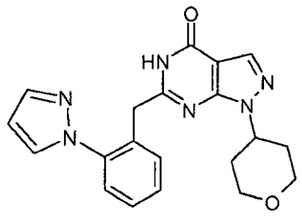
	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 220			1.01 (Method 1)	418 $(M+H)^+$
Example 221			1.24 (Method 1)	413 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 222			1.34 (Method 1)	412 $(M+H)^+$
Example 223			1.03 (Method 1)	473 $(M+H)^+$
Example 224			0.96 (Method 1)	388 $(M+H)^+$
Example 225			1.18 (Method 1)	418 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 226			1.57 (Method 1)	494 $(M+H)^+$
Example 227			1.19 (Method 1)	419 $(M+H)^+$
Example 228			1.26 (Method 1)	406 $(M+H)^+$
Example 229			1.40 (Method 1)	417 $(M+H)^+$
Example 230			1.06 (Method 1)	389 $(M+H)^+$
Example 230-1			1.24 (Method 1)	474 $(M+H)^+$

	structure	starting material	R_t [min]	MS (ESI, m/z)
Example 230-2			1.16 (Method 1)	391 $(M+H)^+$
Example 230-3			1.25 (Method 1)	404 $(M+H)^+$
230-4			1.28 (Method 1)	367 $(M+H)^+$

Example 231



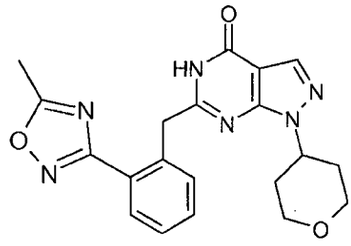
A vial was charged under inert atmosphere with Example 5 (175 mg, 0.45 mmol), pyrazole (306 mg, 4.49 mmol), copper iodide (85 mg, 0.45 mmol) and cesium

carbonate (439 mg, 1.35 mmol) were added. Dimethylformammide (5 ml), previously degassed, was then added, followed by N-N'-dimethylethylenediamine (47.87 µl; 0.45 mmol). The reaction mixture was heated to 120 °C for three hours.The suspension was then filtered over a Celite pad; Celite was washed with DMF. The volume of the organic phase was reduced under reduced pressure and, afterwards, ammonium chloride saturated solution was added, followed by ethyl acetate. The phases were separated and the organic phase was washed with brine and then dried. The crude product was purified by SPE cartridge and the product obtained was further purified by SPE Stratosphere "PL-THIOL MP" to completely remove copper salts. The solid obtained was triturated with diethyl ether. 15.5 mg of the desired compound were obtained (yield = 9.2%).

HPLC-MS (Method 1E hydro): R_t: 7.80 min

MS (ESI pos): m/z = 377 $(M+H)^+$

Example 232



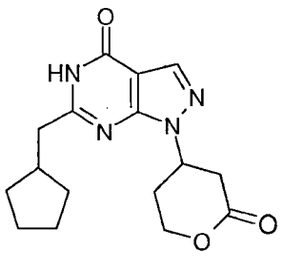
Example 53 (100 mg, 0.298 mmol) and hydroxylamine (0.073 ml, 1.19 mmol) were mixed together in absolute ethanol (4 ml) in a 50 ml flask. The reaction mixture was refluxed for 3 hours before being worked up. The solvent was then removed under reduced pressure to obtain 120 mg (content 70%, 0.228 mmol) of N-Hydroxy-2-[4-oxo-1-(tetrahydro-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylmethyl]-benzamidine as solid that was used as such in the next step.
N-Hydroxy-2-[4-oxo-1-(tetrahydro-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylmethyl]-benzamidine (120 mg, content 70%; 0.228 mmol) was suspended in trimethylorthoacetate (5 ml) and acetic acid was added afterwards (1 ml); the mixture was heated to 100 °C for one hour. The mixture was cooled at room

temperature and the precipitation of a solid was observed. The filtrate was evaporated under reduced pressure; the crude product was purified by flash chromatography. The product was then triturated with diethyl ether. 24 mg of the desired compound were obtained (yield 26.6%).

HPLC/MS (Method 1E hydro)

MS (ESI pos): m/z = 393 $(M+H)^+$

Example 233



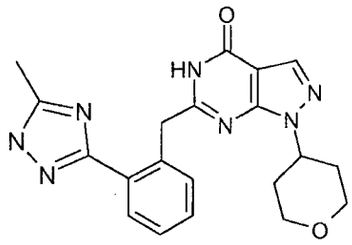
Example 12X (250 mg, 1.14 mmol) was dissolved in 20 ml of hot methanol. Alumina (neutral) was added and the solvent was then removed to give a white powder which was transferred into a 2 ml Wheaton vial; 5,6-Dihydro-2H-pyran-2-oxo was added followed by DMFe (1ml) and the vial was closed tightly. The suspension was heated to 80°C with orbital shaking during 4 days. The reaction was then filtered and the alumina was washed with methanol, ethyl acetate and dicholoromethane; the organic solutions were combined and solvents removed under reduced pressure. The crude product was purified by flash chromatography.

Eluent: (gradient starting with n-hexane/ethyl acetate 9/1 to ethyl acetate (100%) followed by ethyl acetate/methanol 99/1 to 94/6). 70 mg of the desired compound were obtained as solid (19.3 %).

HPLC-MS (Method 2F): R_t: 9.06 min

MS (ESI pos): m/z = 317 $(M+H)^+$

Example 234

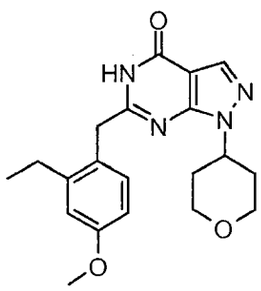


Example 53 (160 mg, content 80% ,0.38 mmol) and hydrazine hydrate (0.186 ml, 3.81 mmol) were mixed together in absolute ethanol (4 ml) in a 25 ml flask. The reaction mixture was refluxed for 6 hours before being worked up. The solvent was removed under reduced pressure to obtain 200 mg (content 70%, 0.38 mmol) of the desired material used as such in the next step. The material (200mg, 70% content, 0.38 mmol) was suspended in trimethylorthoacetate (6 ml). Acetic acid is added (0.6 ml) and the solution was heated to 80°C for 30 minutes. Trimethylortoacetate and acetic acid were removed under reduced pressure and the crude product was partitioned between water and dichloromethane. The organic phase is dried and the crude product purified by flash chromatography. (gradient: starting with dichloromethane/methanol 98/2 and finishing with dichloromethane/methanol 90/10). The product was further purified by trituration with diethyl ether. 8 mg of the desired compound were obtained (4%).

HPLC-MS (Method 1E hydro): R_t: 6.82 min

MS (ESI pos): m/z = 392 $(M+H)^+$

Example 235

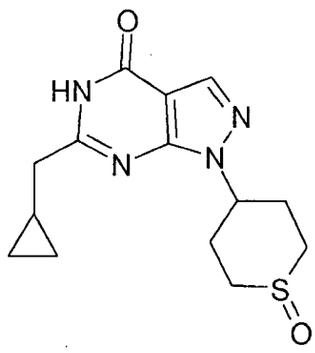


22 mg (0.06 mmol) of example 230-4 in 3 ml methanol were hydrogenated over Pd/C (10 %) under atmospheric pressure. The catalyst was removed. The solvent was evaporated and the residue chromatographed by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield 15.7 mg (71 %) of the product.

HPLC-MS (Method 1): R_t: 1.35 min

MS (ESI pos): m/z = 369 $(M+H)^+$

Example 236

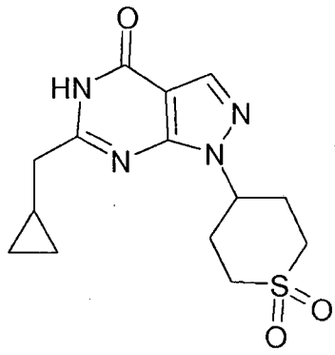


100 mg (73 %, 0.251 mmol) of example 40-5 were dissolved in 2 ml acetic acid and 30 µL (0.35 mmol) hydrogen peroxide solution in water (35 %) were added. The mixture was stirred for 3 h and acetonitrile/water was added. The mixture was chromatographed by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield 50.3 mg (65 %) of the product.

HPLC-MS (Method 1): R_t: 0.88 min

MS (ESI pos): m/z = 307 $(M+H)^+$

Example 237



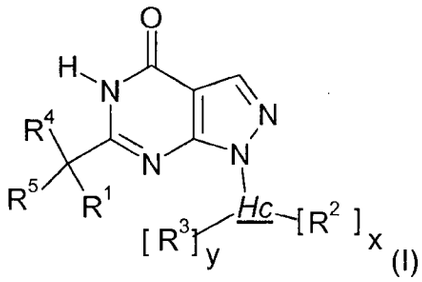
100 mg (73 %, 0.251 mmol) of example 40-5 were dissolved in 2 ml acetic acid and 200 µL (2.33 mmol) hydrogen peroxide solution in water (35 %) were added. The mixture was stirred for 3 days and acetonitrile/water was added. The mixture was chromatographed by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield 21.5 mg (27 %) of the product.

HPLC-MS (Method 1): R_t: 0.93 min

MS (ESI pos): m/z = 323 $(M+H)^+$

Claims

1. A compound according to general formula I



(I)

with

Hc is a mono-, bi- or tricyclic heterocyclyl group, the ring members of which are carbon atoms and at least 1, preferably 1, 2 or 3, heteroatom(s), which are selected from the group of nitrogen, oxygen and sulphur, which is in the form of $-S(O)_r$ - with r being 0, 1 or 2, and

- said heterocyclyl group is or comprises 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member and
- said heterocyclyl group is bound to the scaffold by said 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{2-8}-alkenyl-, C_{2-8}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, aryl-C_{2-6}-alkenyl-, aryl-C_{2-6}-alkynyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, heteroaryl-C_{2-6}-alkenyl-, and heteroaryl-C_{2-6}-alkynyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-O-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, heteroaryl-O-, heteroaryl-C_{1-6}-alkyl-O-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, N-linked-pyridine-2-one-C_{1-6}-alkyl-O-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-O- with C_{3-7}-heterocycloalkyl being bound to O via one of its ring C-atoms, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-O- with C_{3-7}-heterocycloalkyl being bound to the C_{1-6}-alkyl- via one of its ring-C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, R^{10}-CO-O-, $R^{10}O$-CO-O-, $R^{10}O$-CO-O-C_{1-6}-alkyl-, $R^{10}O$-CO-$(R^{10})N$-, $R^{10}O$-CO-$(R^{10})N$-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-$(R^{10})N$-C_{1-6}-alkyl-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-$(R^{10})N$-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, and/or C_{1-6}-alkyl-SO_2-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl-, heteroaryl-, N-linked-pyridine-2-one-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, R^{10}-CO-O-, $R^{10}O$-CO-O-, $R^{10}O$-CO-O-C_{1-6}-alkyl-, $R^{10}O$-CO-$(R^{10})N$-, $R^{10}O$-CO-$(R^{10})N$-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-$(R^{10})N$-, $(R^{10})_2N$-SO_2-$(R^{10})N$-, $(R^{10})_2N$-CO-O-C_{1-6}-alkyl-, $(R^{10})_2N$-CO-$(R^{10})N$-C_{1-6}-alkyl-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-$(R^{10})N$-C_{1-6}-alkyl-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-C_{1-6}-alkyl-, and/or C_{1-6}-alkyl-SO_2-;

R^2 independently of any other **R^2** being selected from the group of:

H-, fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxy-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, preferably C_{1-6}-alkyl-S-C_{2-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, aryl-C_{2-6}-alkenyl-, aryl-C_{2-6}-alkynyl-, heteroaryl-, heteroaryl-C_{1-6}-alkyl-, heteroaryl -C_{2-6}-alkenyl-, heteroaryl -C_{2-6}-alkynyl-, R^{10}-O-C_{2-3}-alkyl-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, R^{10}-O-CO-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-, C_{1-6}-alkyl-SO_2- and oxo,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-,

and in case **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-;

R^3 being selected from the group of

H-, hydroxy and R^{10}-O-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-,

or

R^4 and R^5 together with the carbon atom to which they are bound form a 3- to 6-membered cycloalkyl group,

where the above-mentioned members including the carbocyclic ring formed may optionally be substituted independently of one another by one or more substituents selected from the group consisting of
fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and (C_{1-6}-alkyl-)$_2$N-CO-;

R^{10} independently from any other **R^{10}** being selected from the group of

H- (but not in case it is part of a group being selected from R^{10}O-CO-, R^{10}-SO_2- or R^{10}-CO-), F_3C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-3}-alkyl-, heteroaryl, and heteroaryl-C_{1-3}-alkyl-,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)-, preferably, and in particular preferably in case of (R^{10})$_2$N-CO-, these two R^{10} together with said nitrogen atom they are bound to form a group selected

from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl- and C_{1-6}-alkyl-O-;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof,

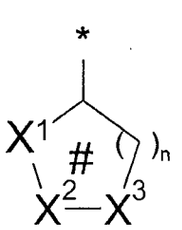
with the proviso for each applicable embodiment of formula I of the invention that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -CH_2-group.

2. A compound according to claim 1, wherein

Hc is a heterocyclyl group according to a formula being selected from the group of formulae I.1, I.2 and I.3:

formula I.1:



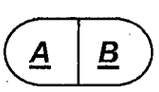
with

n = 1, 2, 3;

X^1, X^2, X^3, independently from each other being CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, or $S(O)_r$ with r = 0, 1, 2, whereby at least one of X^1, X^2, X^3 is O, NH, NR^2 or $S(O)_r$;

#: meaning that the ring is not aromatic, while for n = 1 one bond within the ring system optionally may be a double bond and for n = 2 or n = 3 one bond or two bonds within the ring system optionally may be (a) double bond(s), thereby replacing ring-member bound hydrogen atoms, whereby such double bond(s) preferably being a C-C double bond, more preferably the ring being saturated;

formula I.2:

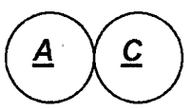


with

A being the ring system of formula I.1;

B being a 3, 4, 5 or 6 membered second ring system that is annelated to ***A*** and that besides the two atoms and one bond - which may be a single or a double bond - it shares with ***A*** consists only of carbon atoms and that may be saturated, partially saturated or aromatic; the substituents $\mathbf{R^2}$ and/or $\mathbf{R^3}$ independently of each other and independently of each x or y may be at ring ***A*** or ring ***B***; whereby the two ring atoms that are shared by the two ring systems ***A*** and ***B*** both may be carbon atoms, both may be nitrogen atoms or one may be a carbon and the other one may be a nitrogen atom, whereby two carbon atoms or one carbon and one nitrogen atom are preferred and two carbon atoms are more preferred;

formula I.3:



with

A, being the ring system of formula I.1;

C being a 3, 4, 5 or 6 membered saturated or partially saturated second ring system that is spiro fused to ***A*** and that besides the one atom it shares with ***A*** consists only of carbon atoms and the substituents R^2 and/or R^3 independently of each other and independently of each x and y may be at ring ***A*** or ring ***C***;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, benzyl-O-, and/or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other **R^2** being selected from the group of

H-, fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine and C_{1-6}-alkyl-,

and in cases **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, or C_{1-6}-alkyl-SO_2-, where these substituents may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and C_{1-6}-alkyl-;

R^3 being selected from the group of

H-, hydroxy, C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, and methyl;

R^{10} independently from any other **R^{10}** being selected from the group of

H- (but not in case it is part of a group being selected from R^{10}O-CO- or R^{10}-CO-), C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, aryl and heteroaryl,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)-, preferably, and in particular preferably in case of $(R^{10})_2$N-CO-, these two R^{10} together with said nitrogen atom they are bound to form a group selected from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1, wherein

Hc is a monocyclic, non-aromatic, saturated heterocyclic group of 4 to 8, preferably 5, 6 or 7 ring atoms, whereby said ring atoms are carbon atoms and 1, 2 or 3 heteroatom(s), preferably 1 heteroatom, the heteroatom(s) being selected from oxygen, nitrogen and sulphur, the sulphur being in the form of $-S(O)_r-$ with r being 0, 1 or 2, preferably with r being 0 and whereby preferably said heterocyclic group being attached to the scaffold by a carbon ring atom which is not directly attached to said ring heteroatom;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, benzyl-O-, and/or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other **R^2** being selected from the group of H- and C_{1-6}-alkyl-,

and in cases **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other **R^2**: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}$-alkyl$)_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, and methyl, preferably both being H;

R^{10} independently from any other R^{10} being C_{1-6}-alkyl-, phenyl, pyridyl and in case R^{10} is a substituent of a nitrogen atom R^{10} is selected from the group of H, C_{1-6}-alkyl-, phenyl and pyridyl,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof,

with the proviso that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no CH_2-group attached to said carbon atom.

4. A compound according to claim 1, wherein

Hc is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl and piperazinyl, more preferably tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and thereof preferably , 3- and 4-tetrahydropyranyl, 3- and 4-piperidinyl and 3- pyrrolidinyl;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-C_{1-6}-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, C_{3-7}-heterocycloalkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, benzyl-O-, and/or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other potential **R^2** being selected from the group of H- and C_{1-6}-alkyl-,

and in cases **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other **R^2**: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}$-alkyl$)_2N$-CO-;

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$\mathbf{R^3}$ being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$\mathbf{R^4}$ and $\mathbf{R^5}$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 being H;

$\mathbf{R^{10}}$ independently from any other $\mathbf{R^{10}}$ being selected from the group of C_{1-6}-alkyl-, phenyl and pyridyl and in case $\mathbf{R^{10}}$ is a substituent of a nitrogen atom $\mathbf{R^{10}}$ is selected from the group of H, C_{1-6}-alkyl-, phenyl and pyridyl,

where the above-mentioned members may optionally be substituted by one or more substituents selected from the group consisting of
fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

5. A compound according to claim 1, wherein

Hc is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl and piperazinyl, whereby preferably the tetrahydropyranyl is 3- or 4-tetrahydropyranyl, the tetrahydrofuranyl is 3-tetrahydrofuranyl, and the piperidinyl is 3- or 4-piperidinyl; more preferably ***Hc*** is tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and thereof preferably , 3- and 4-tetrahydropyranyl, 3- and 4-piperidinyl and 3- pyrrolidinyl;

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, CF_3O-, CF_3-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, HO-C_{1-6}-alkyl-, oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, $(R^{10})_2N$-CO- and/or phenyl,

whereby the oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, CH_3-, CF_3-, CH_3O-, CF_3O-, H_2NCO-, NC-, morpholinyl and/or benzyl-O-;

R^2 independently of any other potential R^2 being selected from the group of H- and C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxyl and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

R^{10} independently from any other **R^{10}** is selected from the group of H, C_{1-6}-alkyl-, phenyl and pyridyl,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x independently from each other **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2. preferably **x** = 0 or 1, more preferably **x** = 0;

y independently from each other **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

6. A compound according to claim 1, wherein

Hc is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, piperazinyl, preferably tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and thereof preferably , 3- and 4-tetrahydropyranyl, 3- and 4-piperidinyl and 3- pyrrolidinyl;

$\mathbf{R^1}$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, CH_3-, CH_3O-, H_2NCO- and/or NC-;

$\mathbf{R^2}$ independently of any other $\mathbf{R^2}$ being selected from the group of H- and C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this $\mathbf{R^2}$ shall be independently of any other $\mathbf{R^2}$: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$\mathbf{R^3}$ being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$\mathbf{R^4}$ and $\mathbf{R^5}$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

7. A compound according to claim 1, wherein

Hc is selected from the group of piperidinyl and pyrrolidinyl, preferably 3- or 4-piperidinyl and 3- pyrrolidinyl;

$\mathbf{R^1}$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, CH_3-, CH_3O-, H_2NCO- and/or NC-;

R^2 independently of any other **R^2** being selected from the group of H- and C_{1-6}-alkyl-,

and in cases **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other **R^2**: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, more preferably **x** = 0;

y independently of any x: **y** = 0, or 1, more preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

8. A compound according to claim 1, wherein

Hc is selected from the group of piperidinyl and pyrrolidinyl, preferably 3- or 4-piperidinyl and 3- pyrrolidinyl;

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of each other selected from the group consisting of NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3- and halogen, the halogen preferably being selected from fluorine, chlorine and bromine.

R^2 independently of any other R^2 being selected from the group of H- and C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

R^4 and R^5 both being H

x = 0 or 1;

y = 0;

and pharmaceutically acceptable salts thereof.

9. A compound according to claim 1, wherein

Hc is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, CH_3-, CH_3O-, H_2NCO- and/or NC-;

R^2 independently of any other **R**^{2} being selected from the group of H- and C_{1-6}-alkyl-,

where the above-mentioned C_{1-6}-alkyl-group(s) may optionally be substituted independently of one another by one or more fluorine substituents;

R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R**^{5} independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, most preferably **x** = 0;

y independently of any x: **y** = 0, or 1, most preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

10. A compound according to claim 1, wherein

Hc is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of each other selected from the group consisting of NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3- and halogen, the halogen preferably being selected from fluorine, chlorine and bromine.

$\mathbf{R^2}$ independently of any other $\mathbf{R^2}$ being selected from the group of H- and C_{1-6}-alkyl-,

where the above-mentioned C_{1-6}-alkyl-group(s) may optionally be substituted independently of one another by one or more fluorine substituents;

$\mathbf{R^3}$ being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$\mathbf{R^4}$ and $\mathbf{R^5}$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably R^4 and R^5 both being H;

x independently of any y: **x** = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, most preferably **x** = 0;

y independently of any x: **y** = 0, or 1, most preferably **y** = 0;

and pharmaceutically acceptable salts thereof.

11. A compound according to claim 1, wherein

Hc is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of each other selected from the group consisting of NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3- and halogen, the halogen preferably being selected from fluorine, chlorine and bromine.

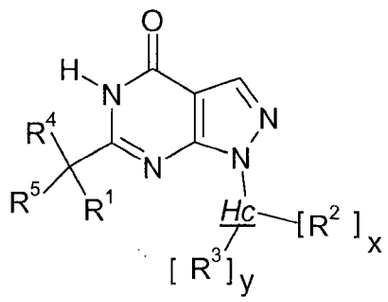
R^4 and R^5 both being H

x = 0;

y = 0;

and pharmaceutically acceptable salts thereof.

12. A compound according to general formula I of claim 1



(I),

wherein;

Hc is a mono-, bi- or tricyclic heterocyclyl group, the ring members of which are carbon atoms and at least 1, preferably 1, 2 or 3, heteroatom(s), which are selected from the group of nitrogen, oxygen and sulphur, which is in the form of $-S(O)_r-$ with r being 0, 1 or 2, and

- said heterocyclyl group is or comprises 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member and
- said heterocyclyl group is bound to the scaffold by said 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member.

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{2-8}-alkenyl-, C_{2-8}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, and heteroaryl-C_{1-6}-alkyl-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-,

HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-O-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, heteroaryl-O-, heteroaryl-C_{1-6}-alkyl-O-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-O- with C_{3-7}-heterocycloalkyl being bound to O via one of its ring C-atoms, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-O- with C_{3-7}-heterocycloalkyl being bound to the C_{1-6}-alkyl- via one of its ring-C-atoms, $(R^{10})_2$N-, $(R^{10})_2$N-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2$N-CO-, $(R^{10})_2$N-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2$N-CO-O-C_{1-6}-alkyl-, $(R^{10})_2$N-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2$N-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2$N-SO_2-, $(R^{10})_2$N-SO_2-C_{1-6}-alkyl-, and C_{1-6}-alkyl-SO_2-,

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl-, heteroaryl-groups mentioned above may optionally be substituted by HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, R^{10}-S-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2$N-, $(R^{10})_2$N-C_{1-6}-alkyl-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2$N-CO-, $(R^{10})_2$N-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-C_{1-6}-alkyl-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2$N-CO-O-, $(R^{10})_2$N-CO-(R^{10})N-, $(R^{10})_2$N-SO_2-(R^{10})N-, $(R^{10})_2$N-CO-O-C_{1-6}-alkyl-, $(R^{10})_2$N-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2$N-SO_2-(R^{10})N-C_{1-6}-alkyl-, $(R^{10})_2$N-SO_2-, $(R^{10})_2$N-SO_2-C_{1-6}-alkyl-, or C_{1-6}-alkyl-SO_2-;

R^2 independently of any other **R^2** being selected from the group of

H-, fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxy-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-

C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{2-3}-alkyl-, $(R^{10})_2N$-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-(R^{10})N-, R^{10}-CO-, $(R^{10})_2N$-CO-(R^{10})N-, R^{10}-SO_2-(R^{10})N-, and C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, C_{1-6}-alkyl-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-,

and in case **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{2-6}-alkynyl-, C_{1-6}-alkyl-S-C_{1-3}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-C_{2-6}-alkynyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkenyl-, C_{3-7}-heterocycloalkyl-C_{2-6}-alkynyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-3}-alkyl-, and $(R^{10})_2N$-CO-;

R^3 independently being selected from the group of H-, hydroxy and R^{10}-O-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, F_3C-, HF_2C-, FH_2C-, and C_{1-3}-alkyl-,

or

R^4 and R^5 together with the carbon atom to which they are bound form a 3- to 6-membered cycloalkyl group,

where the above-mentioned members including the carbocyclic ring formed may optionally be substituted independently of one another by one or more substituents selected from the group consisting of
fluorine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{1-6}-alkyl-O- and (C_{1-6}-alkyl-)$_2$N-CO-;

R^{10} independently from any other **R^{10}** being selected from the group of

H- (but not in case it is part of a group being selected from R^{10}O-CO-, R^{10}-SO_2- or R^{10}-CO-), F_3C-CH_2-, C_{1-6}-alkyl-, C_{2-6}-alkenyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, aryl, aryl-C_{1-3}-alkyl-, heteroaryl, and heteroaryl-C_{1-3}-alkyl-,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)- preferably, and in particular preferably in case of (R^{10})$_2$N-CO-, these two R^{10} groups together with said nitrogen atom they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-C_{1-6}-alkyl-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl- and C_{1-6}-alkyl-O-;

x = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, most preferably **x** = 0;

y = 0, or 1, most preferably **y** = 0;

and pharmaceutically acceptable salt forms or solvates thereof,

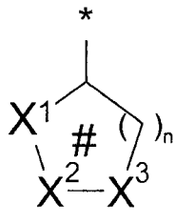
with the proviso that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ spacer.

13. A compound according to claim 12, wherein

Hc is a heterocyclyl group according to a formula being selected from the group of formulae I.1, I.2 and I.3:

formula I.1:



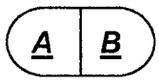
with

n = 1, 2, 3;

X^1, X^2, X^3, independently from each other being CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, or $S(O)_r$ with r = 0, 1, 2, whereby at least one of X^1, X^2, X^3 is O, NH, NR^2 or $S(O)_r$.;

#: meaning that the ring is not aromatic, while for n = 1 one bond within the ring system optionally may be a double bond and for n = 2 or n = 3 one bond or two bonds within the ring system optionally may be (a) double bond(s), thereby replacing ring-member bound hydrogen atoms, whereby such double bond(s) preferably being a C-C double bond, more preferably the ring being saturated;

formula I.2:

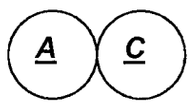


with

A being the ring system of formula I.1;

B being a 3, 4, 5 or 6 membered second ring system that is annelated to ***A*** and that besides the two atoms and one bond - which may be a single or a double bond - it shares with ***A*** consists only of carbon atoms and that may be saturated, partially saturated or aromatic; the substituents R^2 and/or R^3 independently of each other and independently of each x or y may be at ring ***A*** or ring ***B***; whereby the two ring atoms that are shared by the two ring systems ***A*** and ***B*** both may be carbon atoms, both may be nitrogen atoms or one may be a carbon and the other one may be a nitrogen atom, whereby two carbon atoms or one carbon and one nitrogen atom are preferred and two carbon atoms are more preferred;

formula I.3:



with

A, being the ring system of formula I.1;
C being a 3, 4, 5 or 6 membered saturated or partially saturated second ring system that is spiro fused to ***A*** and that besides the one atom it shares with ***A*** consists only of carbon atoms and the substituents R^2 and/or R^3 independently of each other and independently of each x and y may be at ring ***A*** or ring ***C***;

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, aryl and heteroaryl,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-C_{1-6}-alkyl-, $R^{10}O$-CO-O-, and $R^{10}O$-CO-$(R^{10})N$-;

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-groups mentioned above may optionally be substituted by NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other R^2 being selected from the group of

H-, fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine and C_{1-6}-alkyl-,

and in case $\mathbf{R^2}$ is attached to a nitrogen which is a ring member of ***Hc***, this $\mathbf{R^2}$ shall be independently of any other $\mathbf{R^2}$: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and C_{1-6}-alkyl-;

$\mathbf{R^3}$ independently of any other $\mathbf{R^3}$ being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-; preferably $\mathbf{R^3}$ being H-;

$\mathbf{R^4}$ and $\mathbf{R^5}$ independently of one another being selected from the group of H-, fluorine, and methyl; preferably independently of one another being H- or fluorine, more preferably $\mathbf{R^4}$ and $\mathbf{R^5}$ both being H;

$\mathbf{R^{10}}$ independently from any other potential $\mathbf{R^{10}}$ being selected from the group of

C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, aryl and heteroaryl,

and in case where two R^{10} groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -CH_2-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N(C_{3-6}-cycloalkyl)-, -N(C_{3-6}-cycloalkyl-C_{1-4}-alkyl)- or -N(C_{1-4}-alkyl)- preferably, and in particular preferably in case of $(R^{10})_2$N-CO-, these two R^{10} together with said nitrogen they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

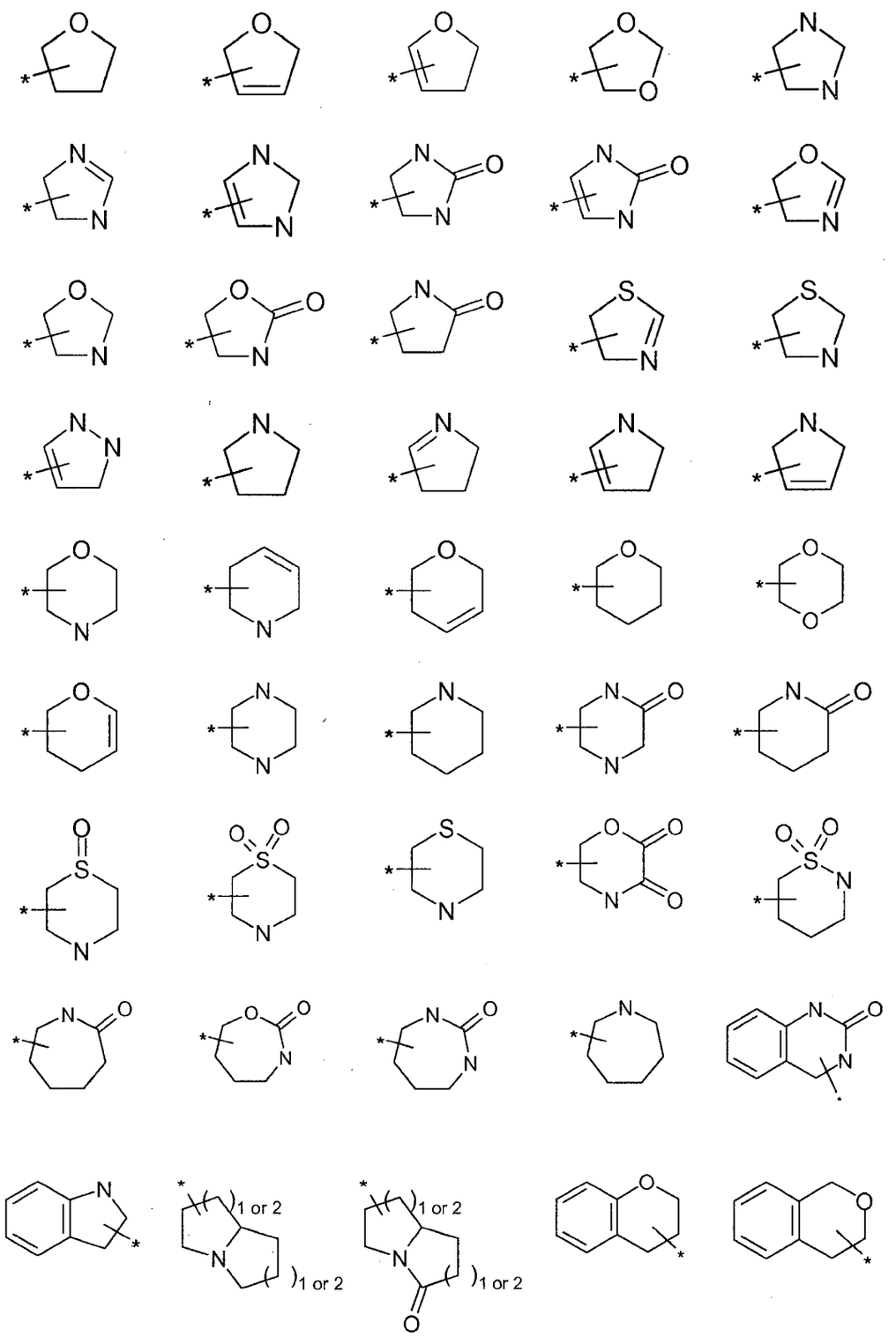
x = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, most preferably **x** = 0;

y = 0, or 1, most preferably **y** = 0;

and pharmaceutically acceptable salt forms or solvates thereof.

14. A compound according to claim 12, wherein

Hc being a heterocyclyl group selected from the group of


1 or 2
1 or 2
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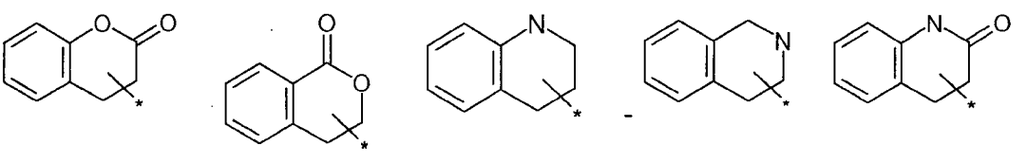
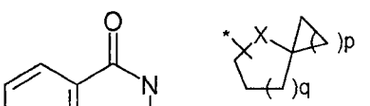
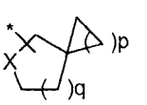
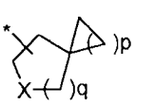




X = O, S or N
p = 1, 2, 3, 4 or 5
q = 1, 2 or 3



X = O, S or N
p = 1, 2, 3, 4 or 5
q = 1, 2 or 3



X = O, S or N
p = 1, 2, 3, 4 or 5
q = 1, 2 or 3

R^1 being selected from the group of

C_{1-8}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-, C_{3-7}-heterocycloalkyl-, aryl and heteroaryl,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-C_{1-6}-alkyl-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-C_{1-6}-alkyl-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-C_{1-6}-alkyl-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-C_{1-6}-alkyl-, R^{10}O-CO-O-, and R^{10}O-CO-(R^{10})N-;

whereby any of the C_{3-7}-cycloalkyl-, C_{3-7}-heterocycloalkyl-, aryl, heteroaryl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-groups mentioned above may optionally be substituted by NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by R^{10}-CO-;

R^2 independently of any other **R^2** being selected from the group of

H-, fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- (preferably C_{2-6}-alkyl), $(R^{10})_2N$-CO-, R^{10}-CO-(R^{10})N-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine and C_{1-6}-alkyl-,

and in case **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, C_{3-7}-cycloalkyl-C_{1-6}-alkyl-, C_{3-7}-heterocycloalkyl-, C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-, aryl, aryl-C_{1-6}-alkyl-, heteroaryl, heteroaryl-C_{1-6}-alkyl-, R^{10}-O-C_{1-3}-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, or C_{1-6}-alkyl-SO_2-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and C1-6-alkyl-;

R^3 being selected from the group of

independently of any other **R^3**: H-, hydroxyl and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

R^4 and **R^5** independently of one another being selected from the group of H-, fluorine, and methyl; preferably independently of one another being selected from the group of H- and fluorine, more preferably **R^4** and **R^5** both being H;

R^{10} independently from any other R^{10} being selected from the group of

C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-, aryl and heteroaryl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-;

x = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, most preferably **x** = 0;

y = 0, or 1, most preferably **y** = 0;

and pharmaceutically acceptable salt forms or solvates thereof

with the proviso that

if ***Hc*** is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -CH_2- spacer.

15. A compound according to claim 13, wherein

Hc being selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl;

and

R^2 independently of any other R^2 being selected from the group of H- and C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2$N-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

and

R^4 and R^5 being H

and

R^{10} independently from any other R^{10} being selected from the group of C_{1-6}-alkyl-, phenyl, and pyridyl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-C_{1-6}-alkyl-, C_{1-6}-alkyl-, and C_{1-6}-alkyl-O-.

16. A compound according to claim 15, wherein

Hc being selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl;

and

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents selected from the group consisting of HO-, NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, C_{3-7}-cycloalkyl-O-, C_{3-7}-cycloalkyl-C_{1-3}-alkyl-O-, CF_3O-, CF_3-, fluorine, chlorine, bromine, C_{3-7}-heterocycloalkyl- and C_{3-7}-heterocycloalkyl-C_{1-6}-alkyl-.

R^2 independently of any other **R^2** being selected from the group of H- and C_{1-6}-alkyl-,

and in cases **R^2** is attached to a nitrogen which is a ring member of ***Hc***, this **R^2** shall be independently of any other **R^2**: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2$N-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

and

R^3 independently of any other **R^3** being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-; preferably **R^3** being H-;

and

R^4 and **R^5** being H

and

x = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, most preferably **x** = 0;

y = 0, or 1, most preferably **y** = 0;

and pharmaceutically acceptable salt forms or solvates thereof.

17. A compound according to claim 1, wherein

Hc being selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl;

and

R^1 being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents selected from the group consisting of NC-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-, CF_3O-, CF_3- and halogen, the halogen preferably being selected from the group of fluorine, chlorine and bromine.

R^2 independently of any other R^2 being selected from the group of H- and C_{1-6}-alkyl-,

and in cases R^2 is attached to a nitrogen which is a ring member of ***Hc***, this R^2 shall be independently of any other R^2: H-, C_{1-6}-alkyl-CO-, C_{1-6}-alkyl-O-CO-, C_{1-6}-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

and

R^3 independently of any other R^3 being selected from the group of

H-, hydroxy and C_{1-6}-alkyl-O-, whereby C_{1-6}-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-; preferably $\mathbf{R^3}$ being H-;

and

$\mathbf{R^4}$ and $\mathbf{R^5}$ being H

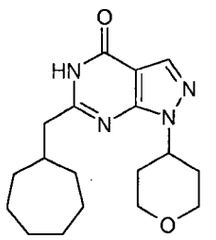
and

x = 0, 1, 2, 3 or 4, preferably **x** = 0, 1 or 2, preferably **x** = 0 or 1, most preferably **x** = 0;

y = 0, or 1, most preferably **y** = 0;

and pharmaceutically acceptable salt forms or solvates thereof.

18. A compound according to claim 1 characterised in that the compound is selected from the group of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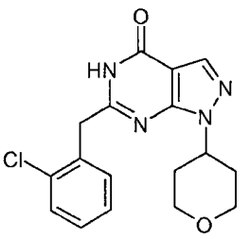
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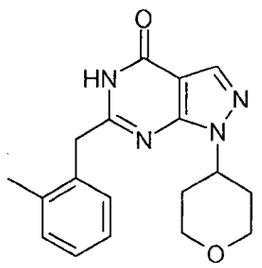
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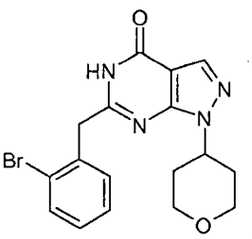
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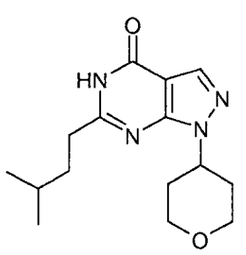
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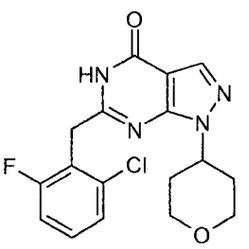
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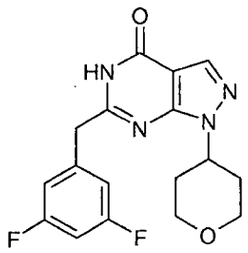
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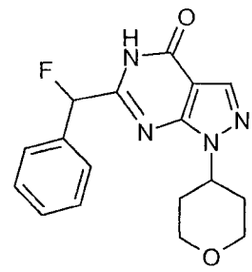
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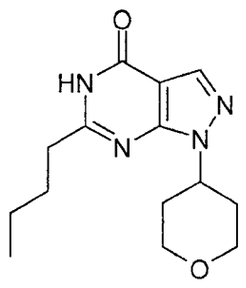
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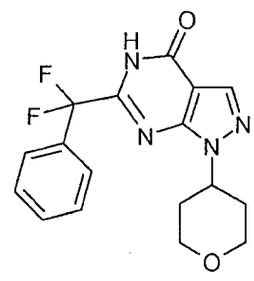
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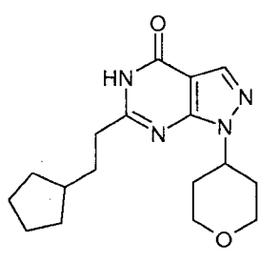
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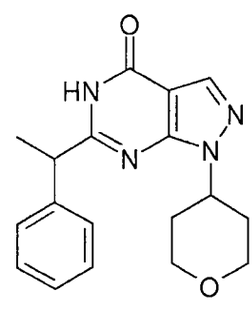
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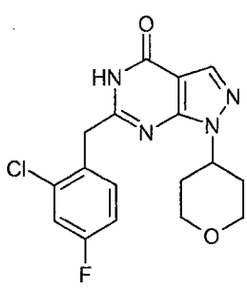
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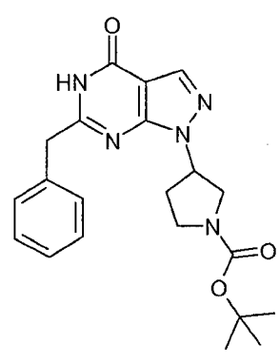
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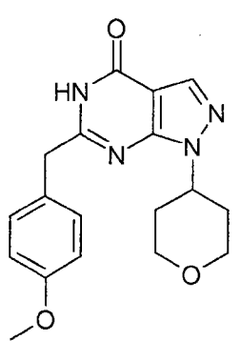
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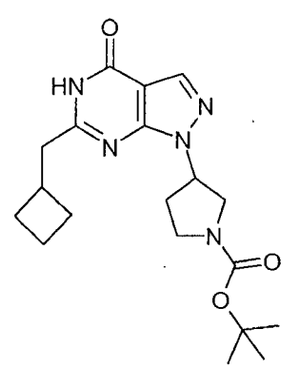
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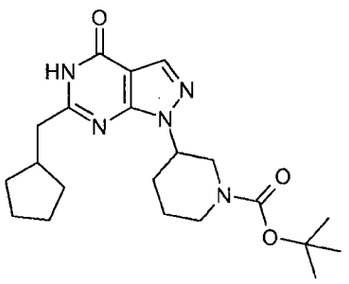

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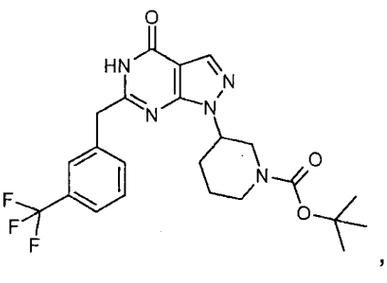

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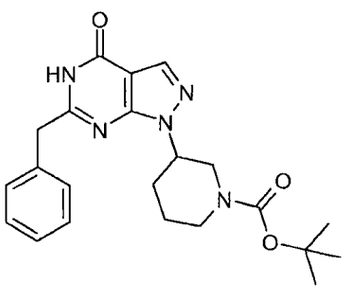

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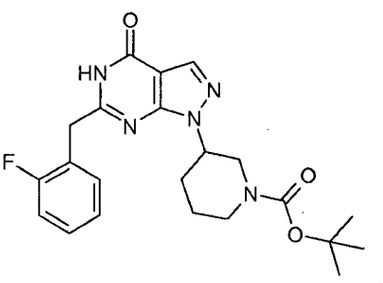

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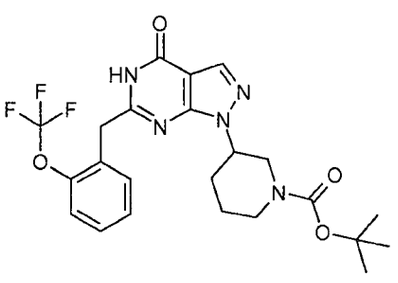

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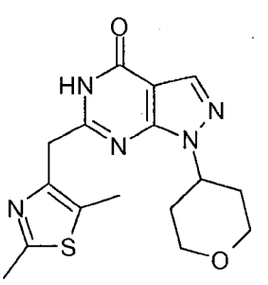

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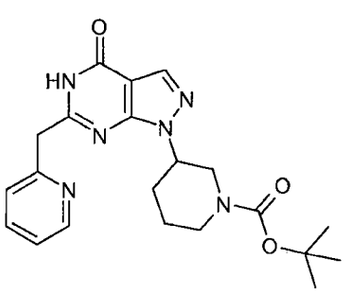

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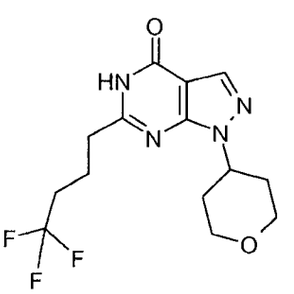

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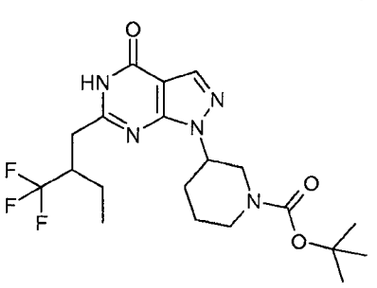

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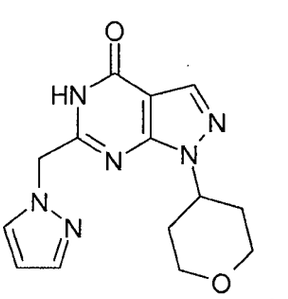

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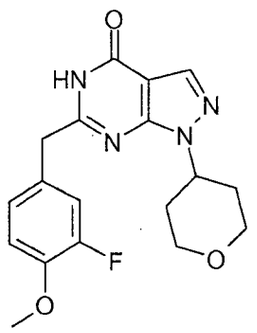

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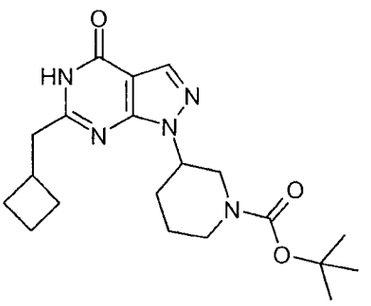

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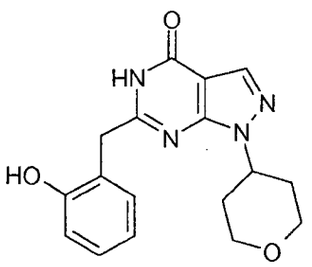

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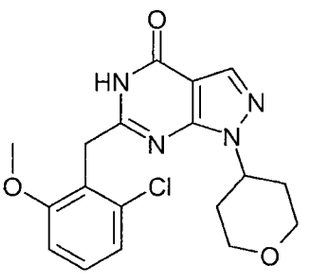

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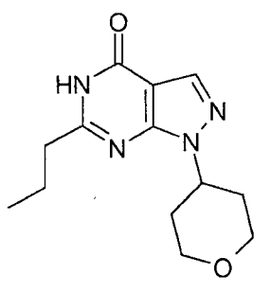

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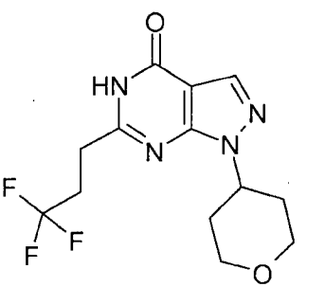

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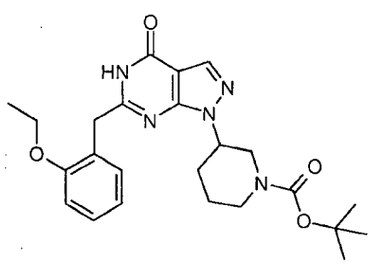

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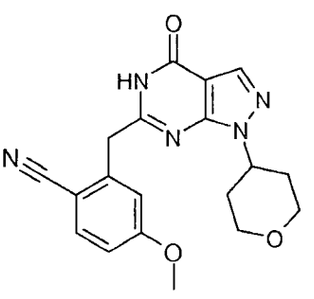

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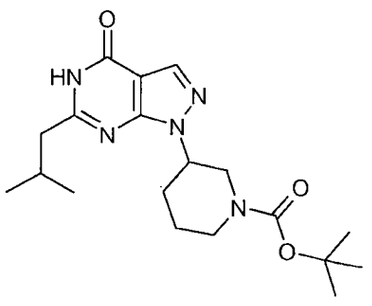

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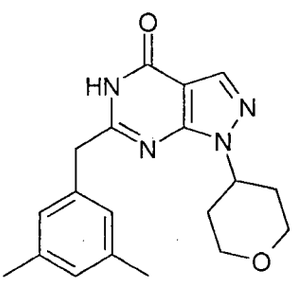

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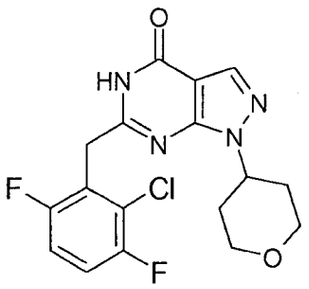

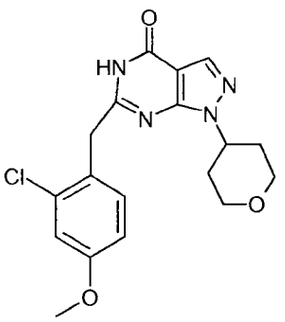

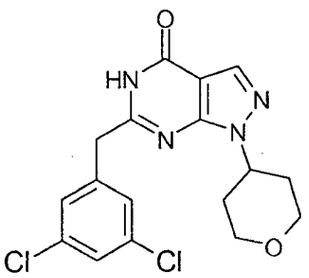

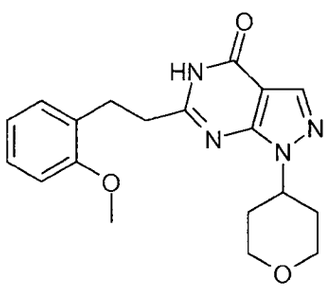

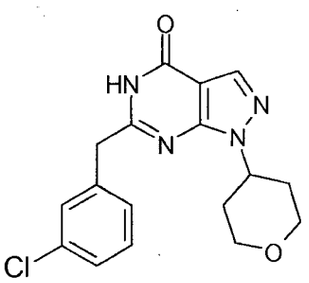

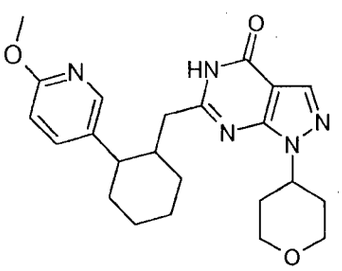

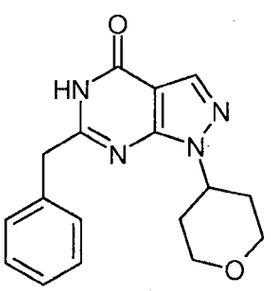

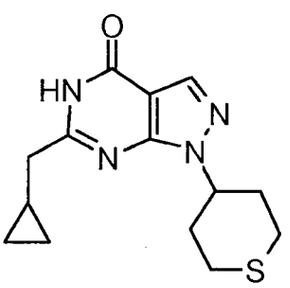

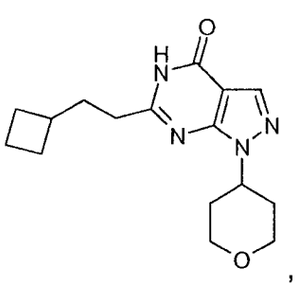

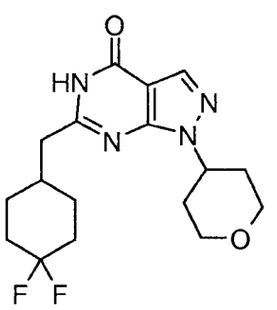

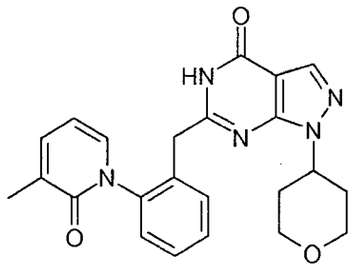

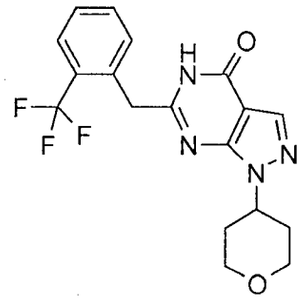

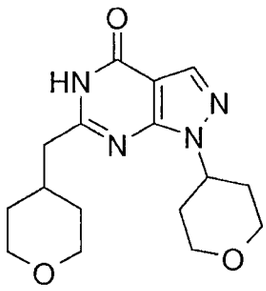

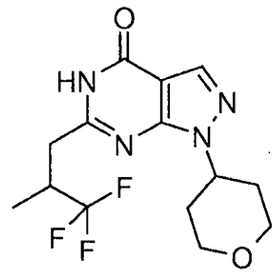

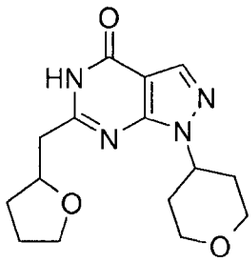

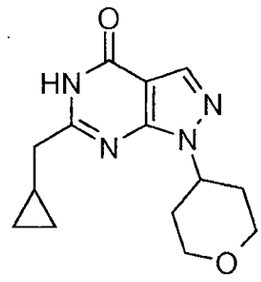

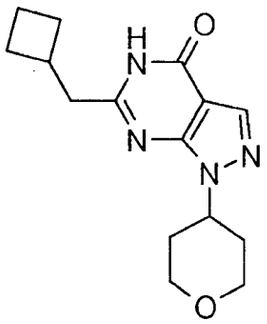

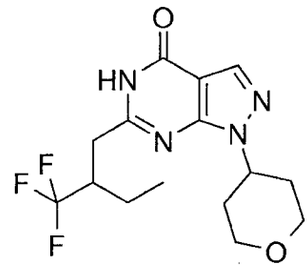

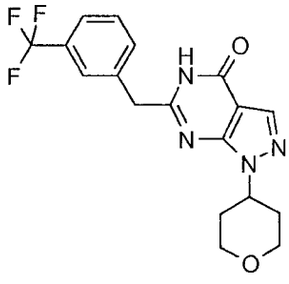

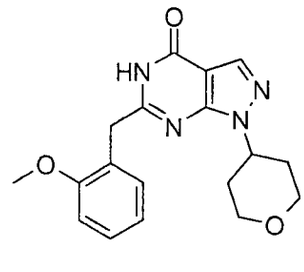

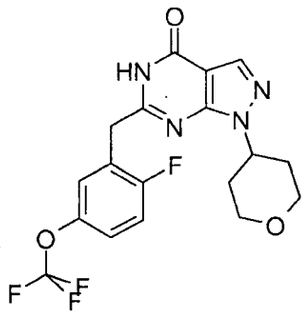

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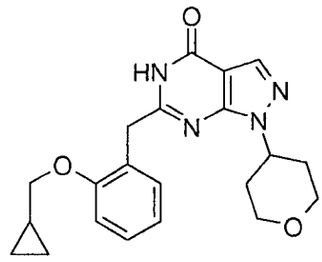

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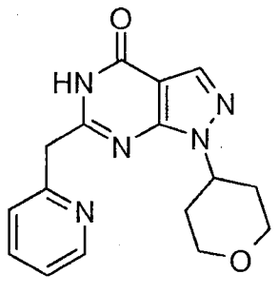

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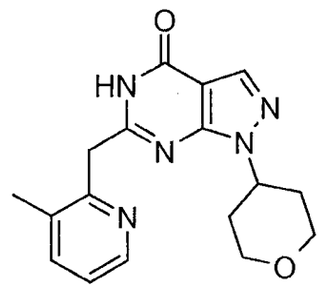

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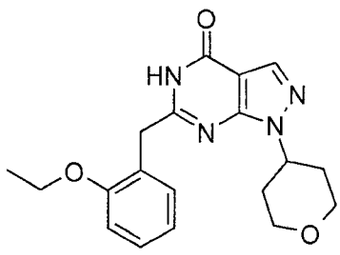

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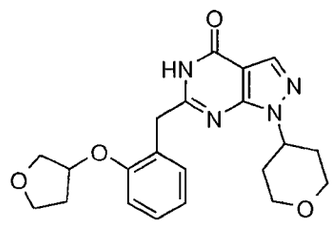

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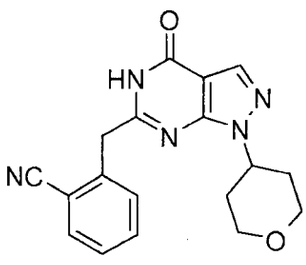

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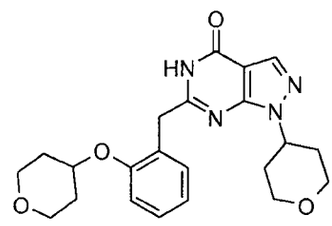

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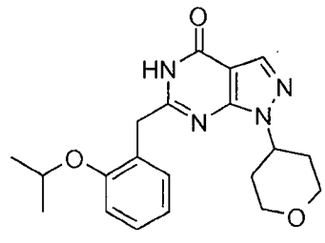

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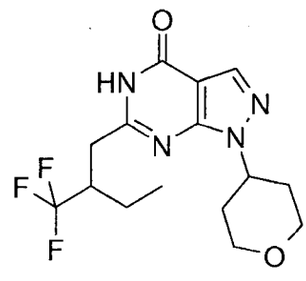

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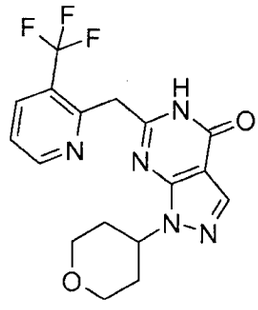

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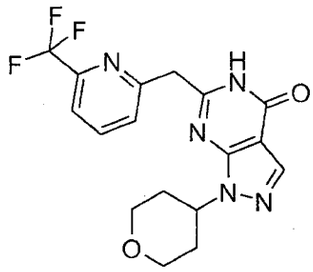

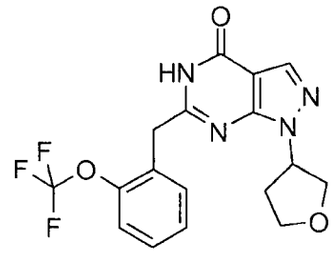

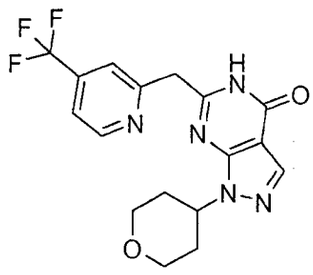

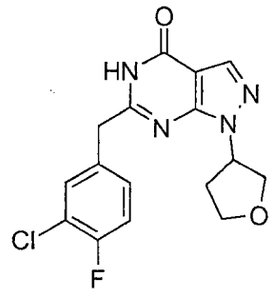

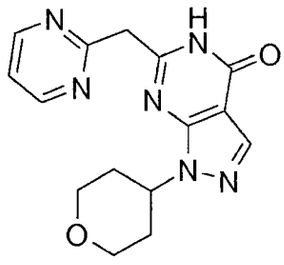

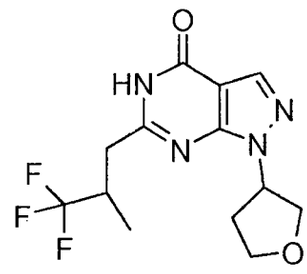

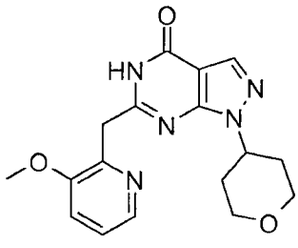

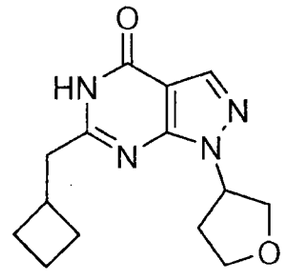

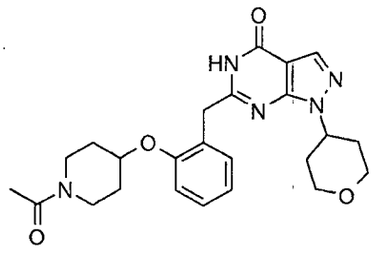

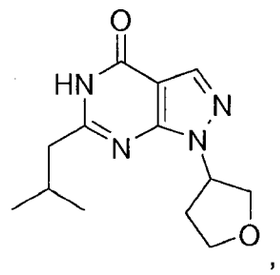

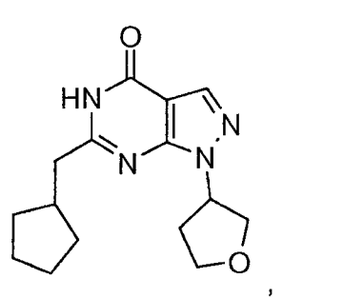

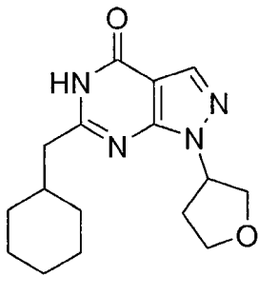

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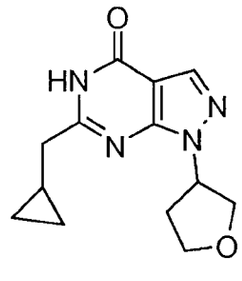

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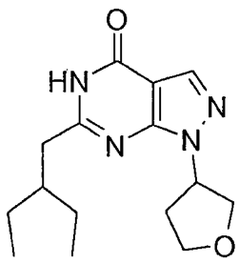

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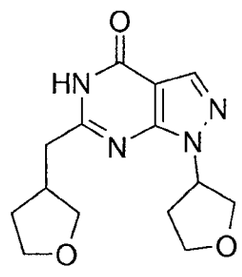

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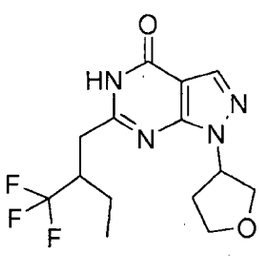

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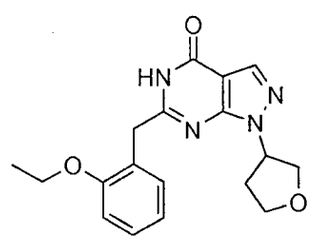

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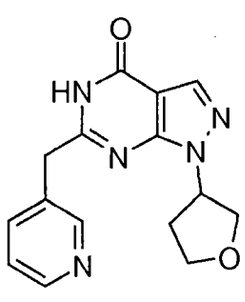

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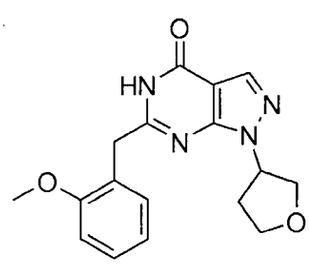

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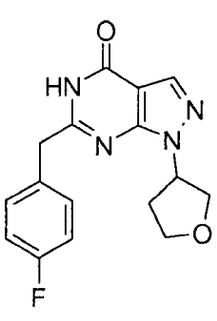

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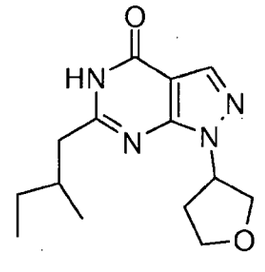

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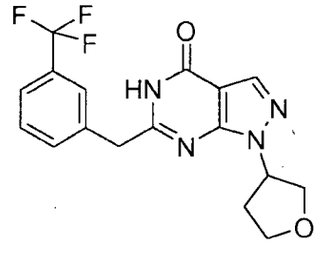

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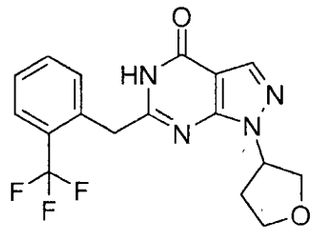

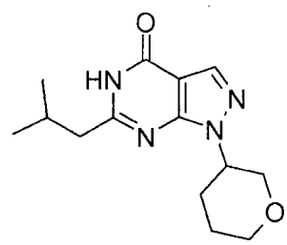

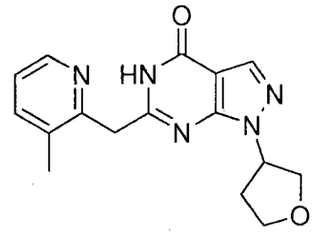

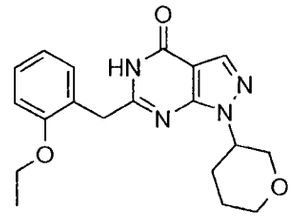

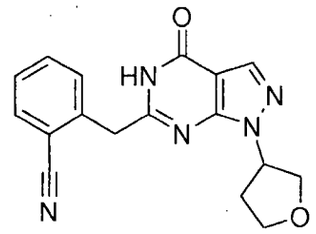

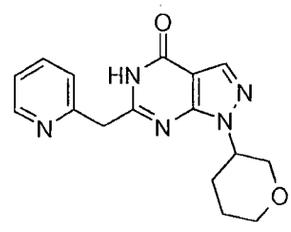

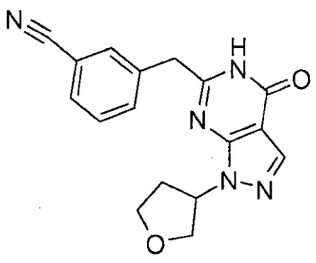

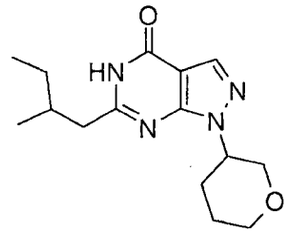

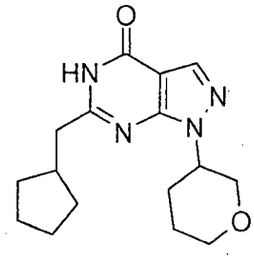

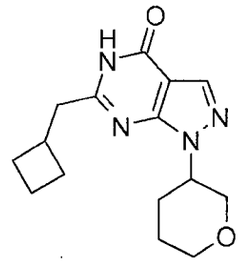

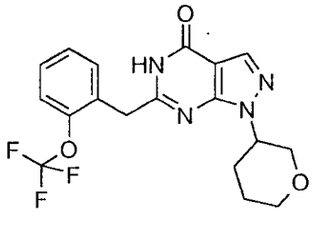

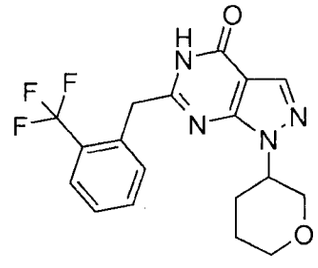

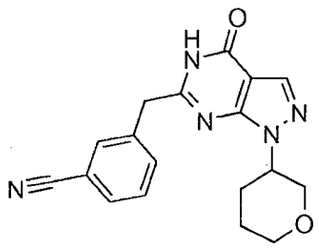

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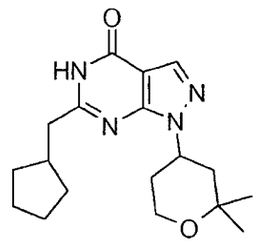

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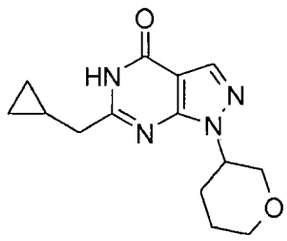

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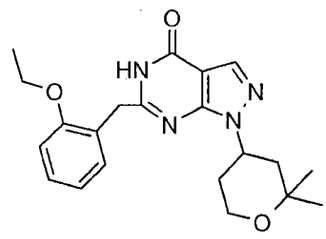

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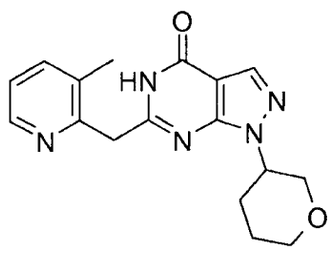

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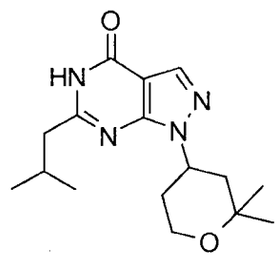

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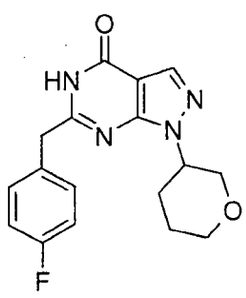

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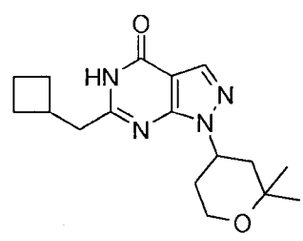

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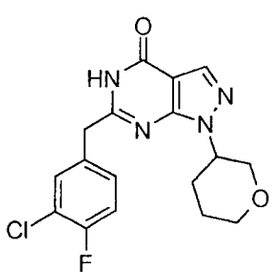

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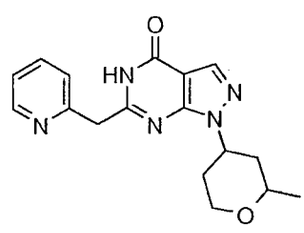

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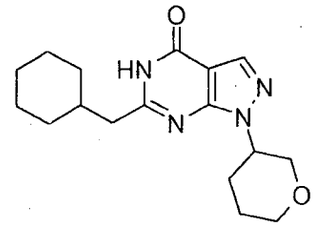

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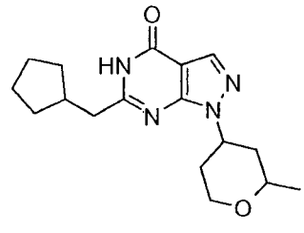

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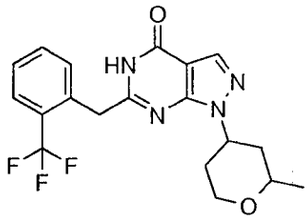
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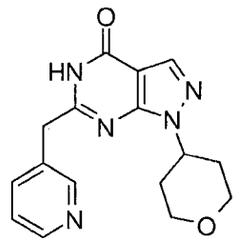
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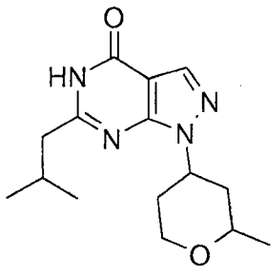
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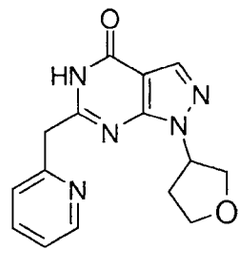
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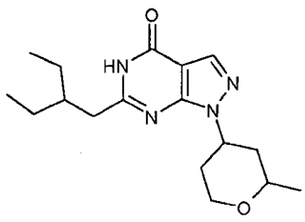
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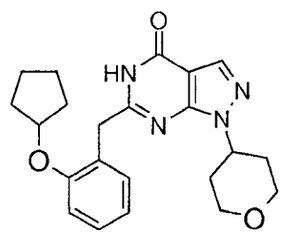
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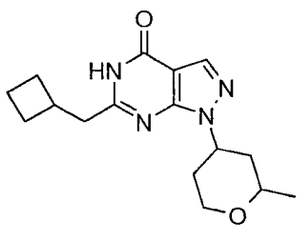
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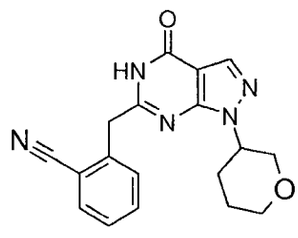
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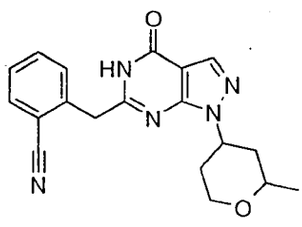
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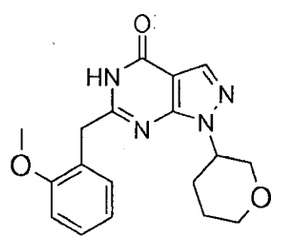
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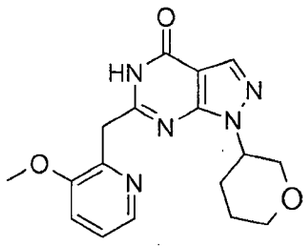
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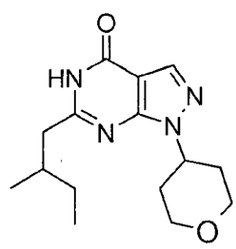
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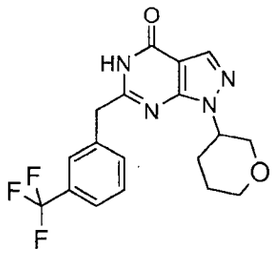
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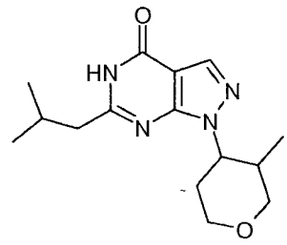
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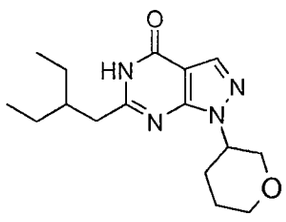
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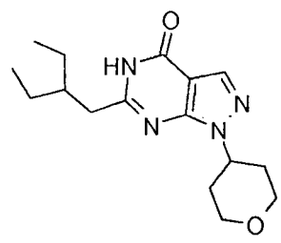
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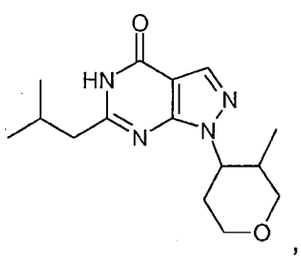
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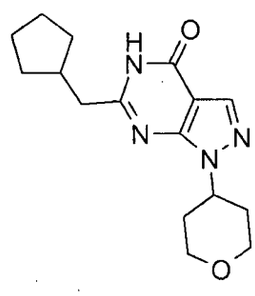
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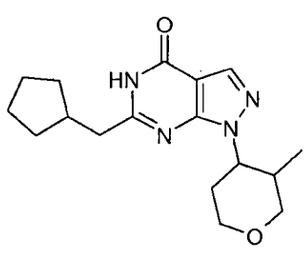
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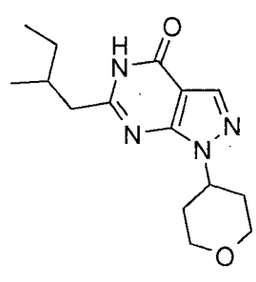
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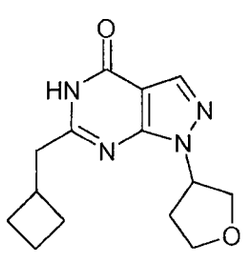
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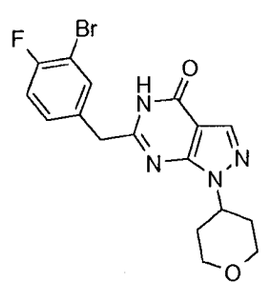
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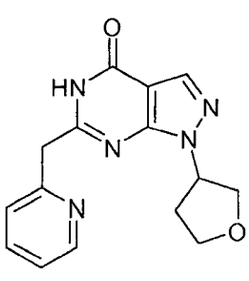
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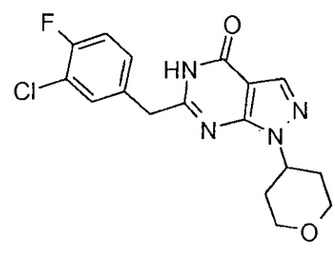
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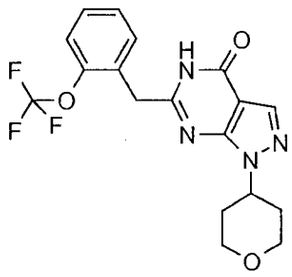
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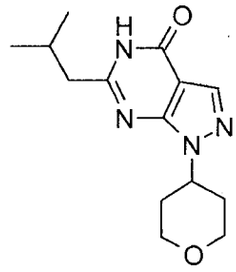
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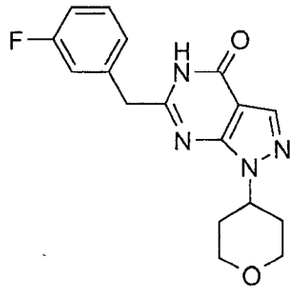
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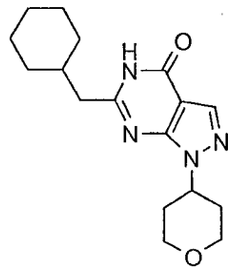
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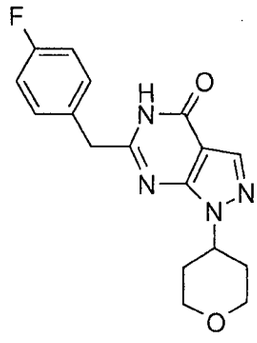
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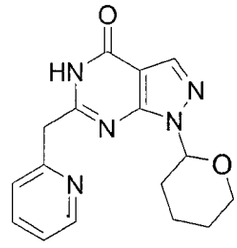
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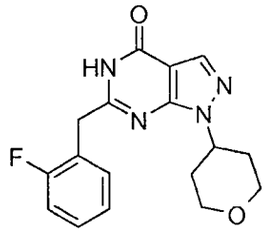
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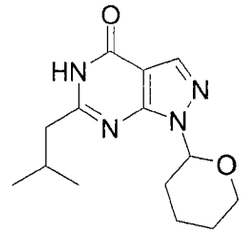
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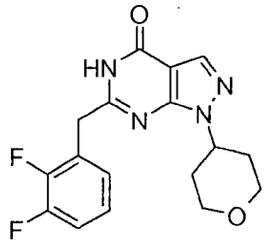
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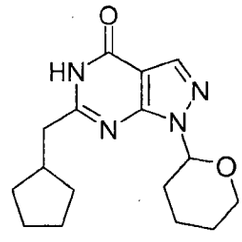
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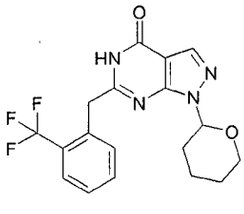
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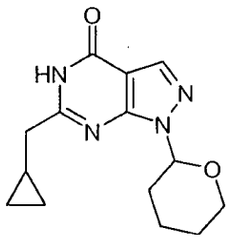

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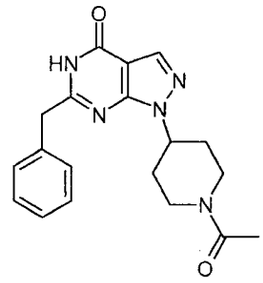

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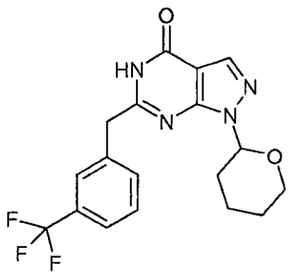

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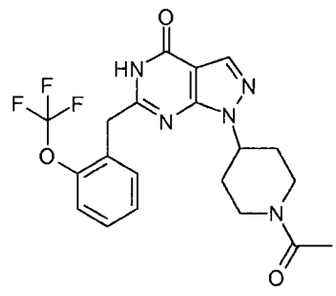

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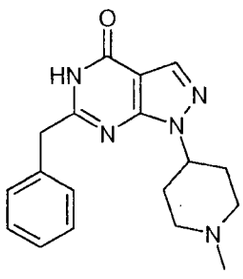

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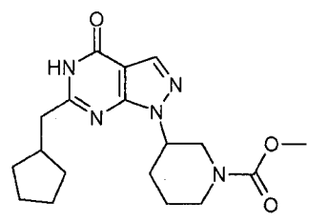

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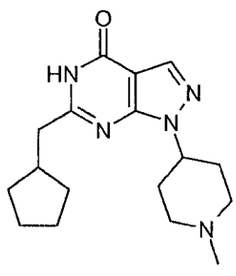

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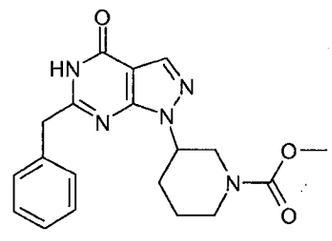

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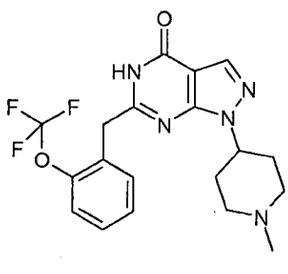

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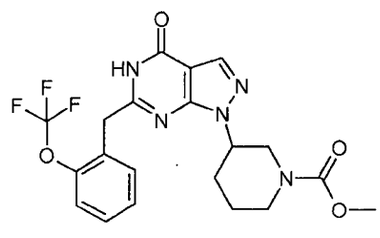

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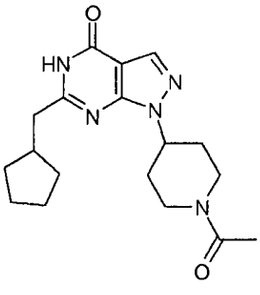

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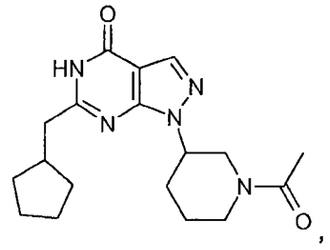

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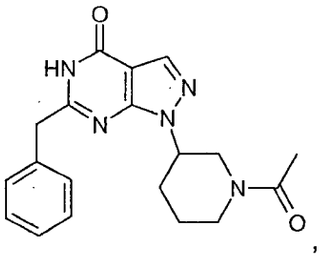
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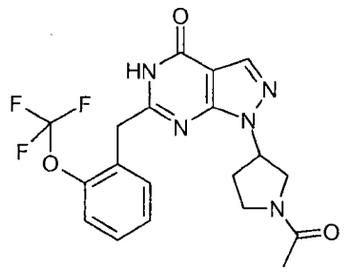
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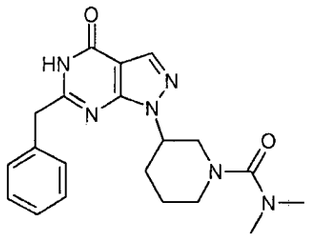
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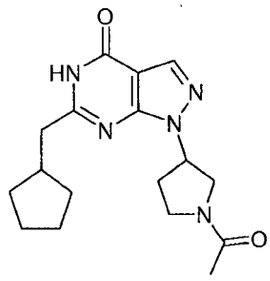
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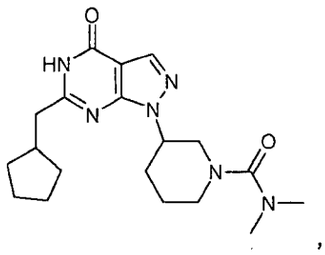
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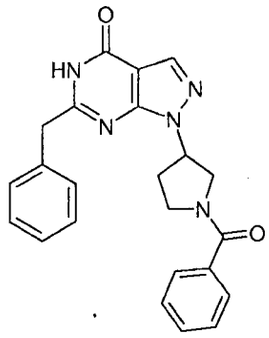
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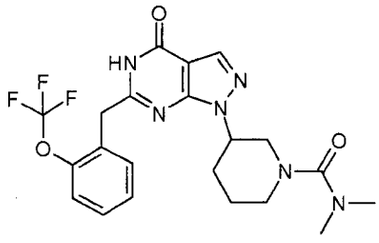
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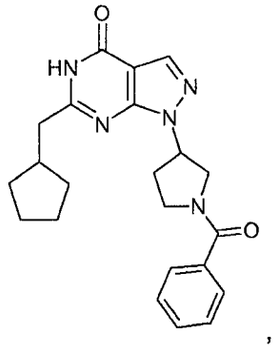
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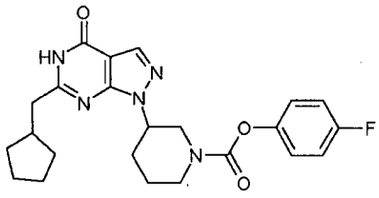
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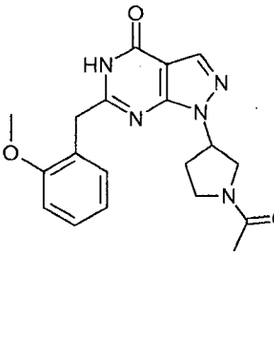
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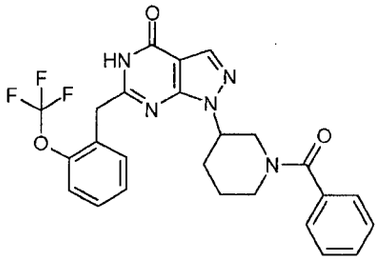
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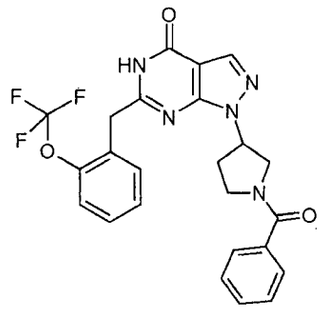

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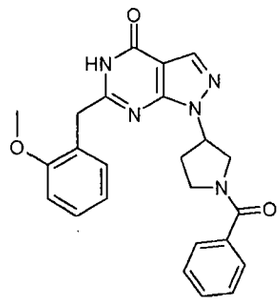

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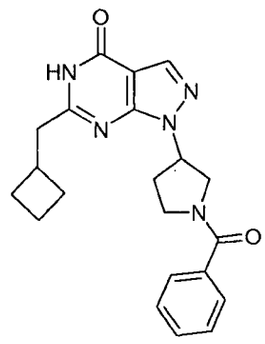

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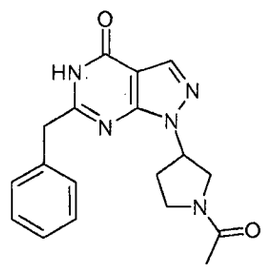

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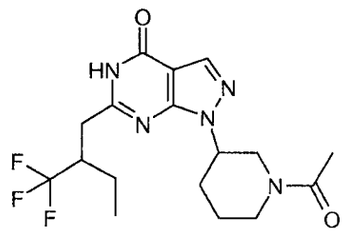

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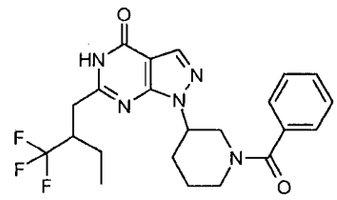

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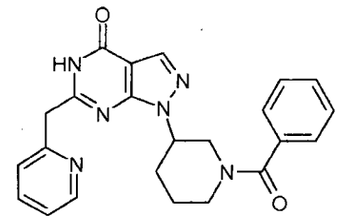

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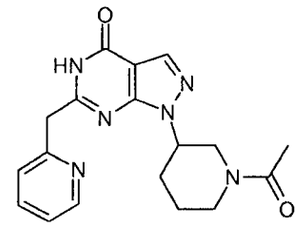

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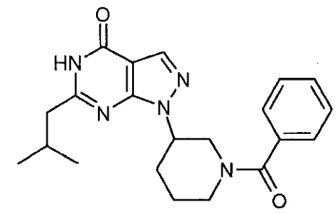

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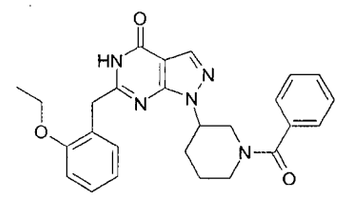

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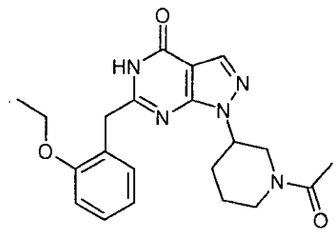

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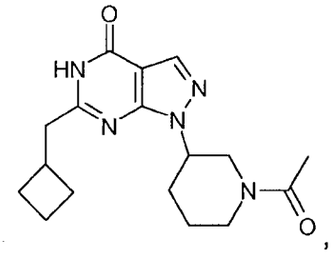

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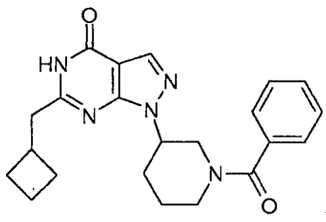

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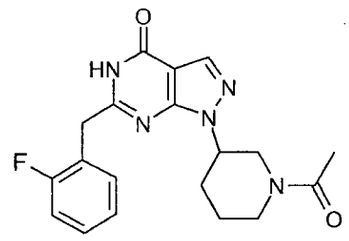

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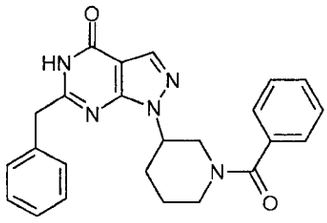

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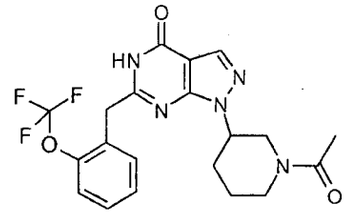

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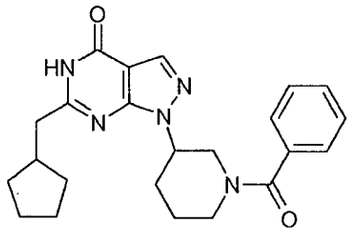

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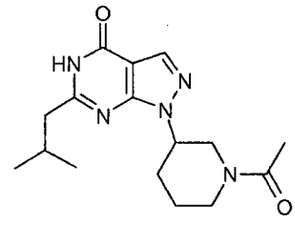

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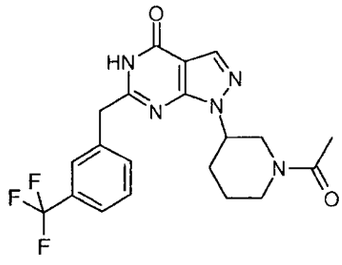

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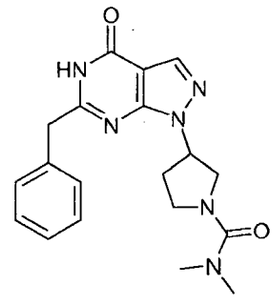

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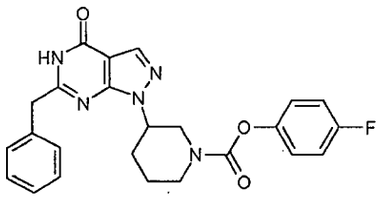

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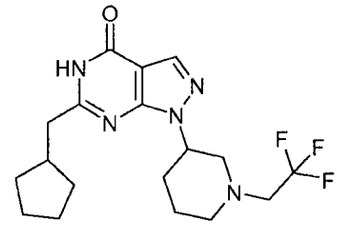

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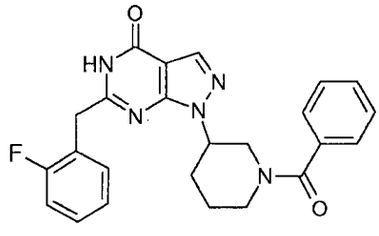

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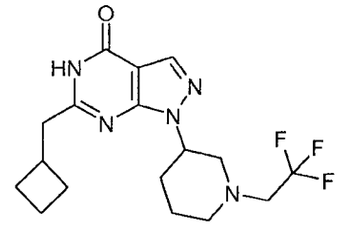

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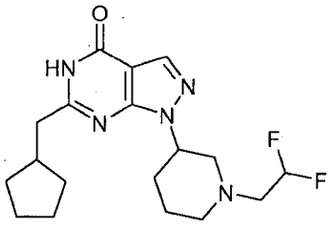

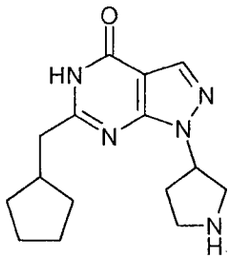

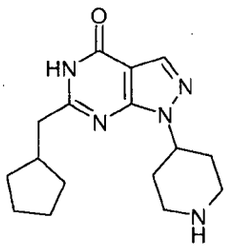

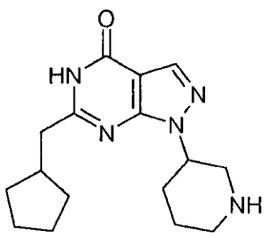

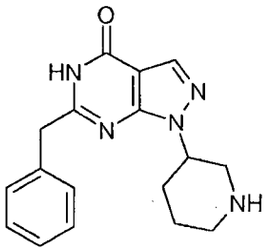

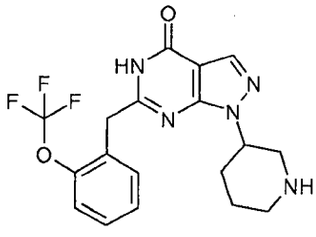

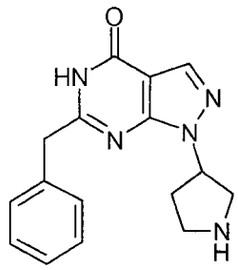

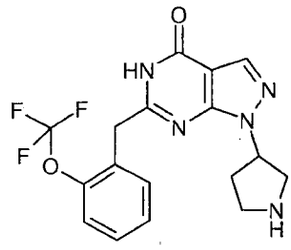

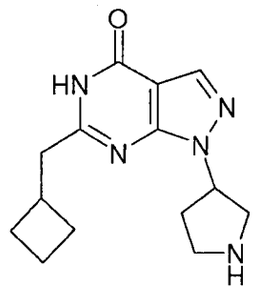

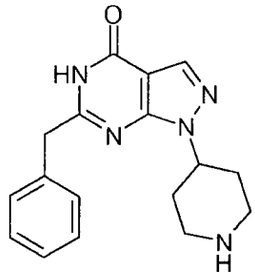

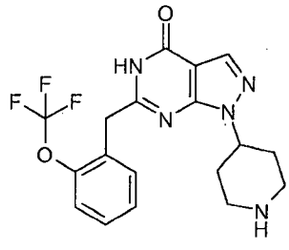

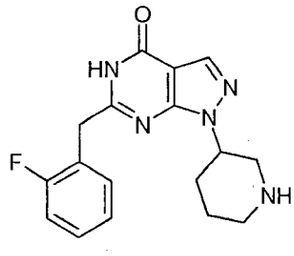

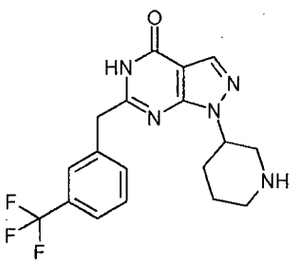

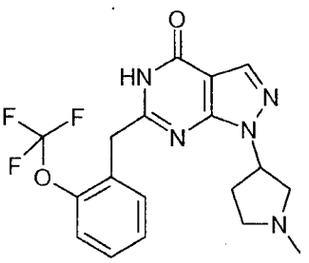

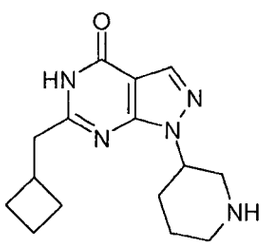

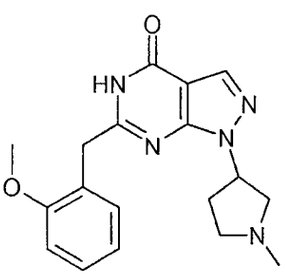

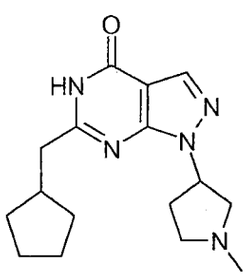

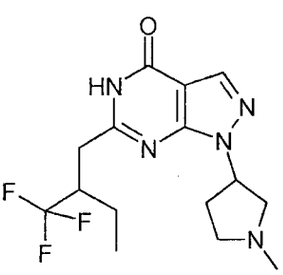

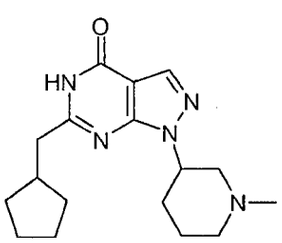

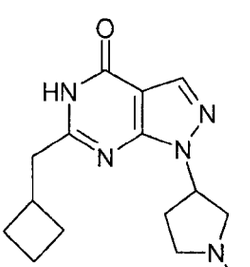

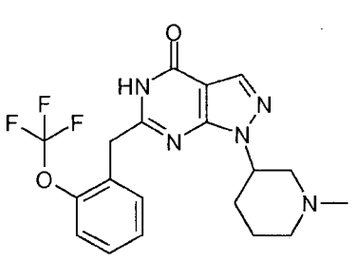

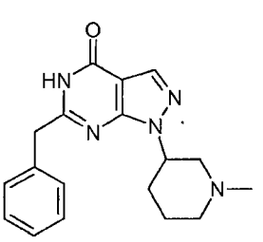

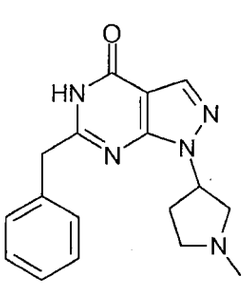

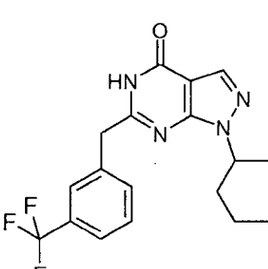

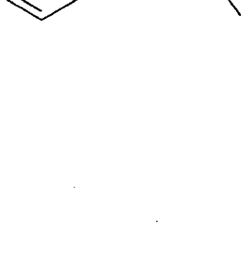

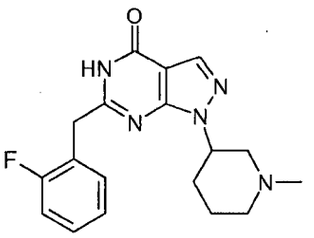

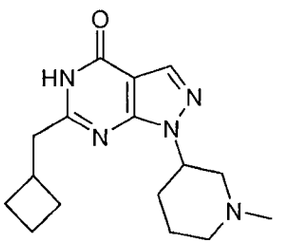

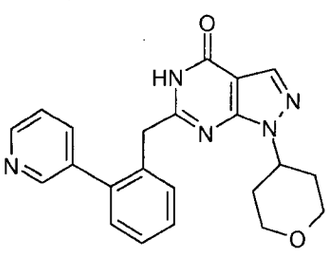

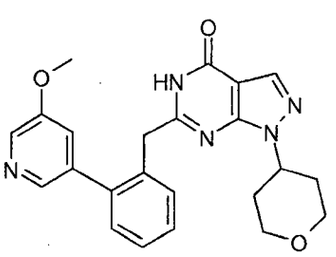

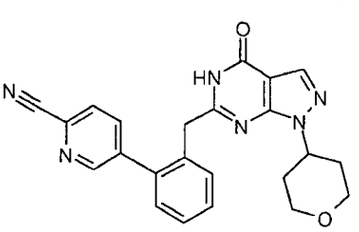

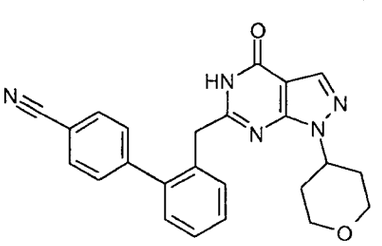

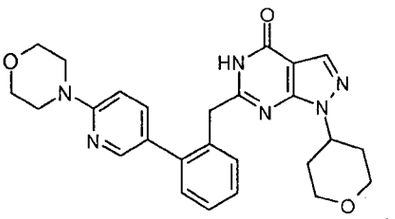

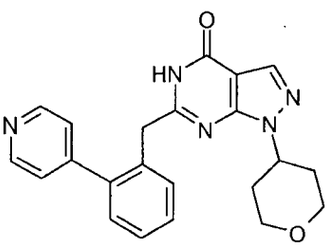

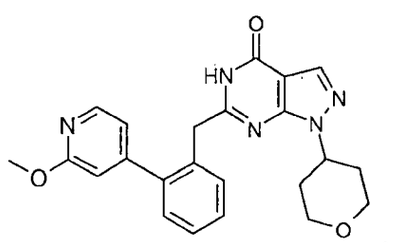

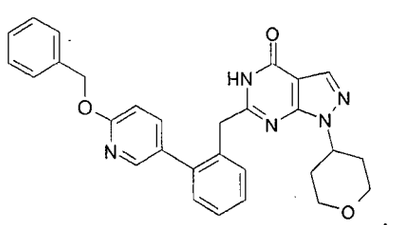

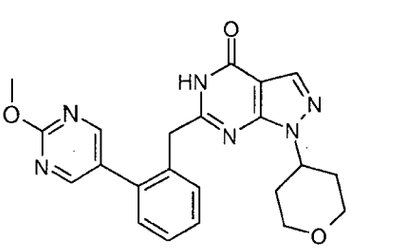

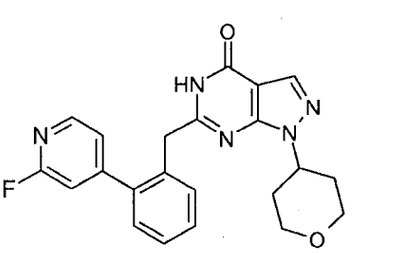

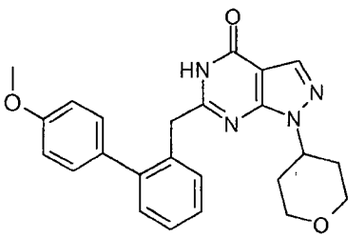
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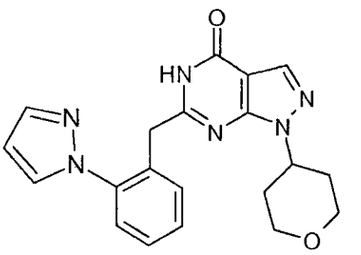
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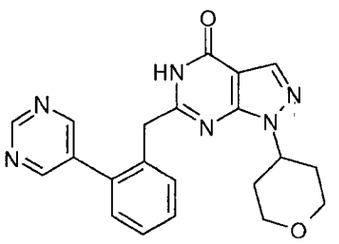
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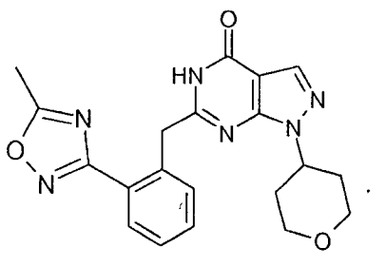
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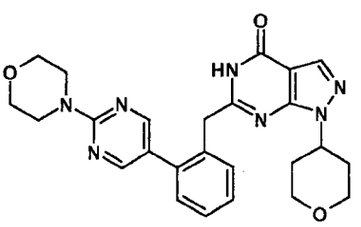
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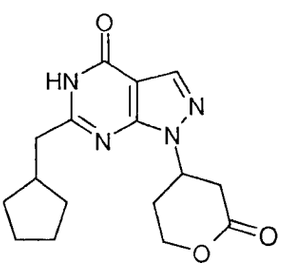
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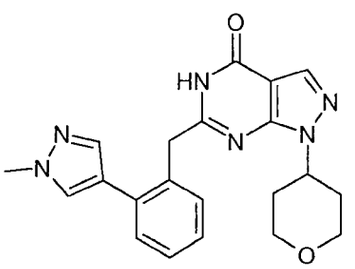
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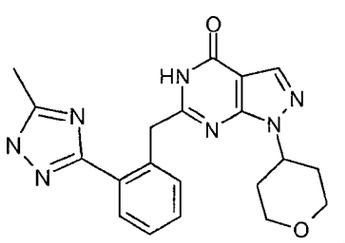
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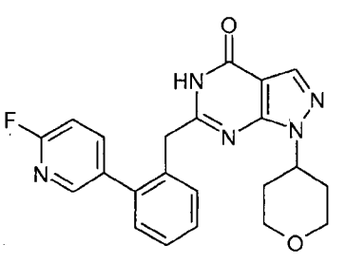
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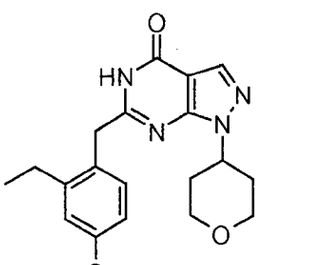
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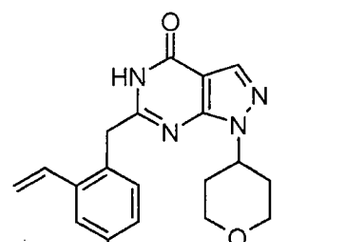
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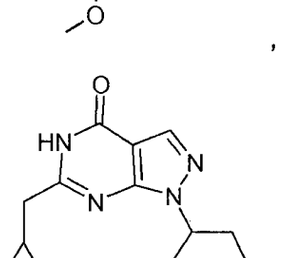
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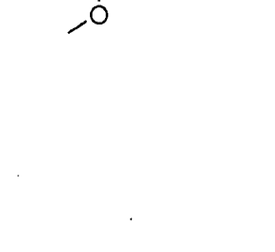
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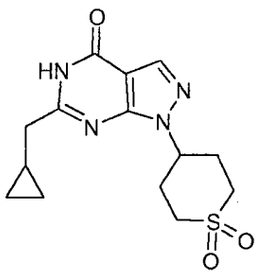

and the stereoisomeres of each thereof or tautomeres of each thereof or solvates of each thereof or pharmaceutically acceptable salts of each thereof.

19. A compound according to any of claims 1 to 18 as a medicament, preferably as a medicament for the treatment of a CNS disease, more preferably as a medicament for the treatment of a CNS disease, the treatment of which is accessible by the inhibition of PDE9.

20. Use of a compound according to claims 1 to 18 for the manufacture of a medicament for the treatment of a disease that is accessible by the inhibition of PDE9.

21. Use of a compound according to any of claims 1 to 18 for the manufacture of medicament for the treatment, amelioration or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

22. Use according to claim 21, characterised in that the medicament is for the treatment, amelioration or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal

lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

23. Use of a compound according to any of claims 1 to 18 for the manufacture of medicament for the treatment of Alzheimer's disease.

24. Use of a compound according to any of claims 1 to 18 for the manufacture of medicament for the treatment of cognitive impairment which is due to Alzheimer's disease.

25. Use of a compound according to any of claims 1 to 18 for the manufacture of medicament for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetis mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

26. Pharmaceutical composition comprising a compound according to any of claims 1 to 18 and a pharmaceutical carrier.

27. Method for the treatment of a condition as defined in any of claims 19 to 25 in a patient comprising administering to said patient a therapeutically active amount of a compound according to any of claims 1 to 18.

28. Combination of a compound according to any of claims 1 to 18 with another active agent for the treatment of Alzheimer's disease.

DERIVADOS DE 1-HETEROCICLILO-1,5-DIHIDRO-PIRAZOLO[3,4-D]PIRIMIDIN-4-ONA Y SU USO COMO MODULADORES DE LA PDE9A

La invención se refiere a nuevas pirazolopirimidinonas disustituidas en 1,6, en las que i.) el átomo de nitrógeno del grupo pirazolo que está próximo al grupo pirimidino está unido a un heterociclo orgánico no aromático, que tiene al menos un heteroátomo en el anillo seleccionado entre O, N y S y ii.) al átomo de C entre los dos átomos de nitrógeno del anillo de pirimidinona está unido un segundo sustituyente mediante un puente de metileno opcionalmente sustituido. Según un aspecto de la invención los nuevos compuestos se destinan a la fabricación de medicamentos, en particular medicamentos para el tratamiento de trastornos relacionados con déficits en la percepción, concentración, aprendizaje o memoria. Los nuevos compuestos se destinan también a la fabricación de medicamentos para el tratamiento de la enfermedad de Alzheimer. Otros aspectos de la presente invención se refieren a un procedimiento para la elaboración de los compuestos y a su uso para producir medicamentos.

ANTECEDENTES DE LA INVENCIÓN

La inhibición de la fosfodiesterasa 9A (PDE9A) es uno de los conceptos actuales para encontrar nuevas rutas de acceso para el tratamiento de los deterioros cognitivos debidos a trastornos del SNC como la enfermedad de Alzheimer o debidos a cualquier otro proceso neurodegenerativo del cerebro. Con la presente invención, se presentan nuevos compuestos que siguen este concepto.

La fosfodiesterasa 9A es un miembro de la amplia familia de las fosfodiesterasas. Estas clases de enzimas modulan los niveles de los nucleótidos cíclicos 5'-3'-adenosina monofosfato cíclico (cAMP) y 5'-3'-guanosina monofosfato cíclico (cGMP). Estos nucleótidos cíclicos (cAMP y cGMP) son segundos mensajeros importantes y, por lo tanto, desempeñan un papel central en las cascadas de transducción de señales celulares. Cada uno de ellos reactiva, entre otros, pero no exclusivamente, las proteína-cinasas. La

proteína-cinasa activada por cAMP se denomina proteína-cinasa A (PKA), y la proteína-cinasa activada por cGMP se denomina proteína-cinasa G (PKG). Las PKA y PKG activadas, son capaces a su vez, de fosforilar una serie de proteínas efectoras celulares (p. ej., canales de iones, receptores acoplados a la proteína G, proteínas estructurales, factores de transcripción). Es posible de este modo que los segundos mensajeros cAMP y cGMP controlen una amplia diversidad de procesos fisiológicos en una amplia variedad de órganos. Sin embargo, los nucleótidos cíclicos son también capaces de actuar directamente sobre las moléculas efectoras. Por lo tanto, se sabe, por ejemplo, que cGMP es capaz de actuar directamente sobre los canales de iones y, en consecuencia, es capaz de influir en la concentración de iones celulares (revisión en: Wei *et al.*, *Prog. Neurobiol.*, **1998**, *56*, 37-64). Las fosfodiesterasas (PDE) son un mecanismo de control para controlar la actividad de cAMP y cGMP y de este modo controlar a su vez los correspondientes procesos fisiológicos. Las PDE hidrolizan los monofosfatos cíclicos hasta los monofosfatos inactivos AMP y GMP. Actualmente, se han definido 11 familias de PDE sobre la base de la homología de secuencias de los correspondientes genes. Los genes PDE individuales dentro de una familia se diferencian con letras (p. ej., PDE1A y PDE1B). Si ocurren también diferentes variantes de corte y empalme dentro de un gen, esto se indica entonces con una numeración adicional después de las letras (p. ej., PDE1A1).

La PDE9A humana fue clonada y secuenciada en 1998. La identidad de aminoácidos con otras PDE no excede del 34 % (PDE8A) y nunca es menor del 28 % (PDE5A). Con una constante de Michaelis-Menten (Km) de 170 nanomolar, la PDE9A posee gran afinidad hacia cGMP. Además, la PDE9A es selectiva para cGMP (Km para cAMP=230 micromolar). La PDE9A no tiene ningún dominio de unión a cGMP, lo que da a entender que la actividad enzimática no está regulada por cGMP. Se demostró en un análisis de transferencia Western que la PDE9A está expresada en los seres humanos, entre otros, en los testículos, en el cerebro, intestino delgado, músculo esquelético, corazón, pulmón, timo y bazo. La expresión más alta se encontró en el cerebro, intestino delgado, riñón, próstata, colon y bazo (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564; Wang *et al.*, *Gene*, **2003**, *314*, 15-27). El gen para la PDE9A humana se localiza en el cromosoma 21q22.3 y

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comprende 21 exones. Se han identificado 4 variantes alternativas de corte y empalme de la PDE9A (Guipponi *et al.*, *Hum. Genet.*, **1998**, *103*, 386-392). Los inhibidores de PDE clásicos no inhiben la PDE9A humana. Por lo tanto, IBMX, SKF94120, dipiridamol, rolipram y vinpocetina no muestran inhibición sobre la enzima aislada en concentraciones de hasta 100 micromolar. Se ha demostrado una IC_{50} de 35 micromolar para el zaprinast (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564).

La PDE9A murina fue clonada y secuenciada en 1998 por Soderling *et al.* (*J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). Ésta tiene, al igual que la forma humana, gran afinidad para cGMP con una Km de 70 nanomolar. Se encontró una expresión particularmente alta en el riñón, cerebro, pulmón e hígado del ratón. La PDE9A murina tampoco es inhibida por IBMX en concentraciones inferiores a 200 micromolar; la IC50 de zaprinast es 29 micromolar (Soderling *et al.*, *J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). Se ha encontrado que la PDE9A está fuertemente expresada en algunas regiones del cerebro de la rata. Éstas incluyen el bulbo olfatorio, el hipocampo, la corteza, los ganglios basales y el cerebro anterior basal (Andreeva *et al.*, *J. Neurosci.*, **2001**, *21* (22), 9068-9076). El hipocampo, la corteza y el cerebro anterior basal en particular, desempeñan un importante papel en los procesos de aprendizaje y de memoria.

Como ya se ha mencionado antes, la PDE9A se distingue por tener una afinidad particularmente alta hacia cGMP. La PDE9A es por lo tanto activa, incluso a bajas concentraciones fisiológicas, en contraste con la PDE2A (Km=10 micromolar; Martins *et al.*, *J. Biol. Chem.*, **1982**, *257*, 1973-1979), PDE5A (Km=4 micromolar; Francis *et al.*, *J. Biol. Chem.*, **1980**, *255*, 620-626), la PDE6A (Km=17 micromolar; Gillespie and Beavo, *J. Biol. Chem.*, **1988**, *263* (17), 8133-8141) y la PDE11A (Km=0,52 micromolar; Fawcett *et al.*, *Proc. Nat. Acad. Sci.*, **2000**, *97* (7), 3702-3707). En contraste con la PDE2A (Murashima *et al.*, *Biochemistry*, **1990**, *29*, 5285-5292), la actividad catalítica de la PDE9A no es incrementada por cGMP, ya que no tiene dominio GAF (dominio de unión a cGMP mediante el cual se aumenta alostéricamente la actividad de la PDE) (Beavo *et al.*, *Current Opinion in Cell Biology*, **2000**, *12*, 174-179). Los

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inhibidores de la PDE9A pueden, por consiguiente, llevar a un aumento de la concentración basal de cGMP.

Este perfil pondrá en evidencia que la PDE9A interviene en procesos fisiológicos específicos de una manera única y característica, que distingue el papel de la PDE9A de forma característica de cualquiera de los otros miembros de la familia de PDE.

El documento WO04099210 describe pirazolopirimidinonas sustituidas con arilmetilo en 6, que son inhibidores de la PDE9. Los compuestos no tienen un resto heterocíclico no aromático en la posición 1 de la pirazolopirimidina.

El documento WO04096811 describe biciclos heterocíclicos como inhibidores de la PDE9 para el tratamiento de la diabetes, incluyendo la diabetes tipo 1 y tipo 2, la hiperglucemia, dislipidemia, deterioro de la tolerancia a la glucosa, síndrome metabólico, y/o enfermedad cardiovascular.

Otra técnica anterior se dirige a derivados nucleósidos químicamente similares. Como ejemplos se refiere al documento WO02057425, que describe derivados nucleósidos, que son inhibidores de la RNA polimerasa viral dependiente del RNA, o al documento WO01060315, que describe derivados nucleósidos para el tratamiento de la infección de hepatitis C o al documento EP679657, que describe compuestos que sirven como análogos ribonucleósidos o al documento US2002058635, que describe compuestos L-nucleósidos de purina, en los que tanto los anillos de purina como el azúcar están modificados, o funcionalizados, o ambas cosas. Así el azúcar por ejemplo debe presentar al menos un grupo OH esterificado.

El documento WO06084281 describe inhibidores de la enzima de activación E1 que tienen un resto de sulfonamida.

El documento WO05051944 describe nucleósidos que contienen oxetano, para el tratamiento de trastornos relacionados con análogos de nucleósidos tales como los trastornos que implican proliferación e infección celular.

El documento WO9840384 describe pirazolopirimidinonas que son inhibidores de PDE1, 2 y 5, y se pueden emplear para el tratamiento de trastornos cardiovasculares y cerebrovasculares, y trastornos del aparato urogenital.

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Los documentos CH396 924, CH396 925, CH396 926, CH396 927, DE1147234, DE1149013, GB937726 describen pirazolopirimidinonas que tienen un efecto dilatador de las coronarias y que se pueden emplear para el tratamiento de trastornos del flujo sanguíneo del miocardio.

El documento US3732225 describe pirazolopirimidinonas que tienen un efecto antiinflamatorio y reductor de la glucosa sanguínea.

El documento DE2408906 describe estirilpirazolopirimidinonas que se pueden emplear como agentes antimicrobianos y antiinflamatorios para el tratamiento, por ejemplo, del edema.

OBJETIVO DE LA INVENCIÓN

La técnica anterior citada pone de manifiesto que los cambios en el modelo de sustitución de las pirazolopirimidinonas dan como resultado interesantes cambios relacionados con la actividad biológica, respectivamente cambios en la afinidad hacia diferentes enzimas objetivos.

Por lo tanto, es un objetivo de la presente invención proporcionar compuestos que modulen eficazmente la PDE9A con el fin de desarrollar un medicamento, en particular, para enfermedades cuyo tratamiento es accesible mediante la modulación de la PDE9A.

Es otro objetivo de la presente invención proporcionar compuestos que sean útiles para la fabricación de un medicamento para el tratamiento de trastornos del SNC.

Otro objetivo más de la presente invención es proporcionar compuestos que muestren un mejor perfil de efectos colaterales, en comparación con los compuestos de la técnica anterior.

Otro objetivo de la presente invención es proporcionar compuestos que tienen un perfil selectivamente favorable para la inhibición de la PDE9A sobre otros miembros de la familia de PDE y por esto pueden tener ventajas con respecto a los compuestos de la técnica anterior.

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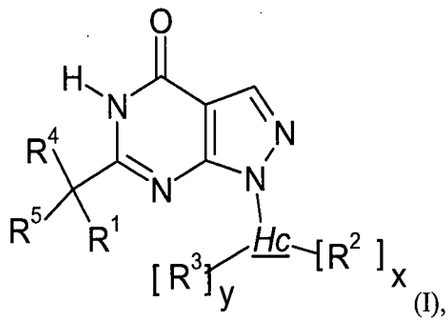
Incluso otro objetivo es proporcionar un medicamento de este tipo no sólo para el tratamiento sino también para la prevención o modificación de la enfermedad correspondiente.

DESCRIPCIÓN DETALLADA DE LA PRESENTE INVENCIÓN

Los compuestos de la presente invención se caracterizan por la fórmula general I:



(I),

con las siguientes definiciones (los sustituyentes se imprimirán en letra negrita para una mejor lectura):

El sustituyente ***Hc*** se define por las siguientes definiciones **Hc^i**, en las que el índice i describe el orden de preferencia, ascendiendo desde **Hc^1** a más preferiblemente (esto es, **Hc^2**), y así sucesivamente:

Hc^1:

Hc es un grupo heterociclilo mono-, bi- o tricíclico, cuyos miembros del anillo son átomos de carbono y al menos 1, preferiblemente 1, 2 o 3, heteroátomos, que se seleccionan del grupo de nitrógeno, oxígeno y azufre, que está en la forma de $-S(O)_r-$ siendo r 0, 1 o 2, y

- dicho grupo heterociclilo es o comprende 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo y

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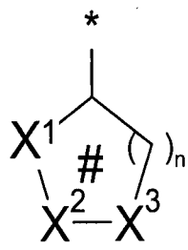
- dicho grupo heterociclilo está unido a la estructura química (scaffold) por dicho 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo.

Hc^{2}:

Hc es un grupo heterociclilo según cualquiera de las fórmulas I.1 o I.2 o I.3:

fórmula I.1:



en la que

n = 1, 2, 3;

X^1, X^2, X^3, son independientemente uno de otro, CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, o $S(O)_r$ siendo r = 0, 1, 2, donde al menos uno de X^1, X^2, X^3 es O, NH, NR^2 o $S(O)_r$.

#: significa que el anillo no es aromático y cuando n = 1, un enlace dentro del sistema de anillos puede ser opcionalmente un doble enlace y cuando n = 2 o n = 3 un enlace o dos enlaces dentro del sistema de anillos pueden ser opcionalmente dobles enlaces, con los que se reemplazan los átomos de hidrógeno unidos a los miembros del anillo. Para cada ocasión el doble enlace es preferiblemente un doble enlace C-C. Preferiblemente el sistema de anillos es saturado.

El * representa el punto de unión al átomo de nitrógeno del anillo pirazolo de la fórmula I.

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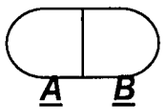
fórmula I.2:



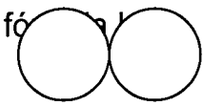
en la que

A es el sistema de anillos de la fórmula I.1;

B es un segundo sistema de anillos de 3, 4, 5 o 6 miembros que está anillado con ***A*** y que aparte de los dos átomos y un enlace que comparte con ***A*** consiste solamente en átomos de carbono y que puede ser saturado, parcialmente saturado o aromático; los sustituyentes R^2 y/o R^3 independientemente uno de otro e independientemente de cada x e y, pueden estar en el anillo ***A*** o en el anillo ***B***;

Los dos átomos del anillo que son compartidos por los dos sistema de anillos ***A*** y ***B*** pueden ser ambos átomos de C, pueden ser ambos átomos de N o uno puede ser un átomo de C y el otro puede ser un átomo de N. Preferiblemente son dos átomos de C, o un átomo de C y un átomo de N, y más preferiblemente son dos átomos de C. El enlace compartido puede ser un enlace sencillo o un enlace doble.

fórmula I.3



A ***C***

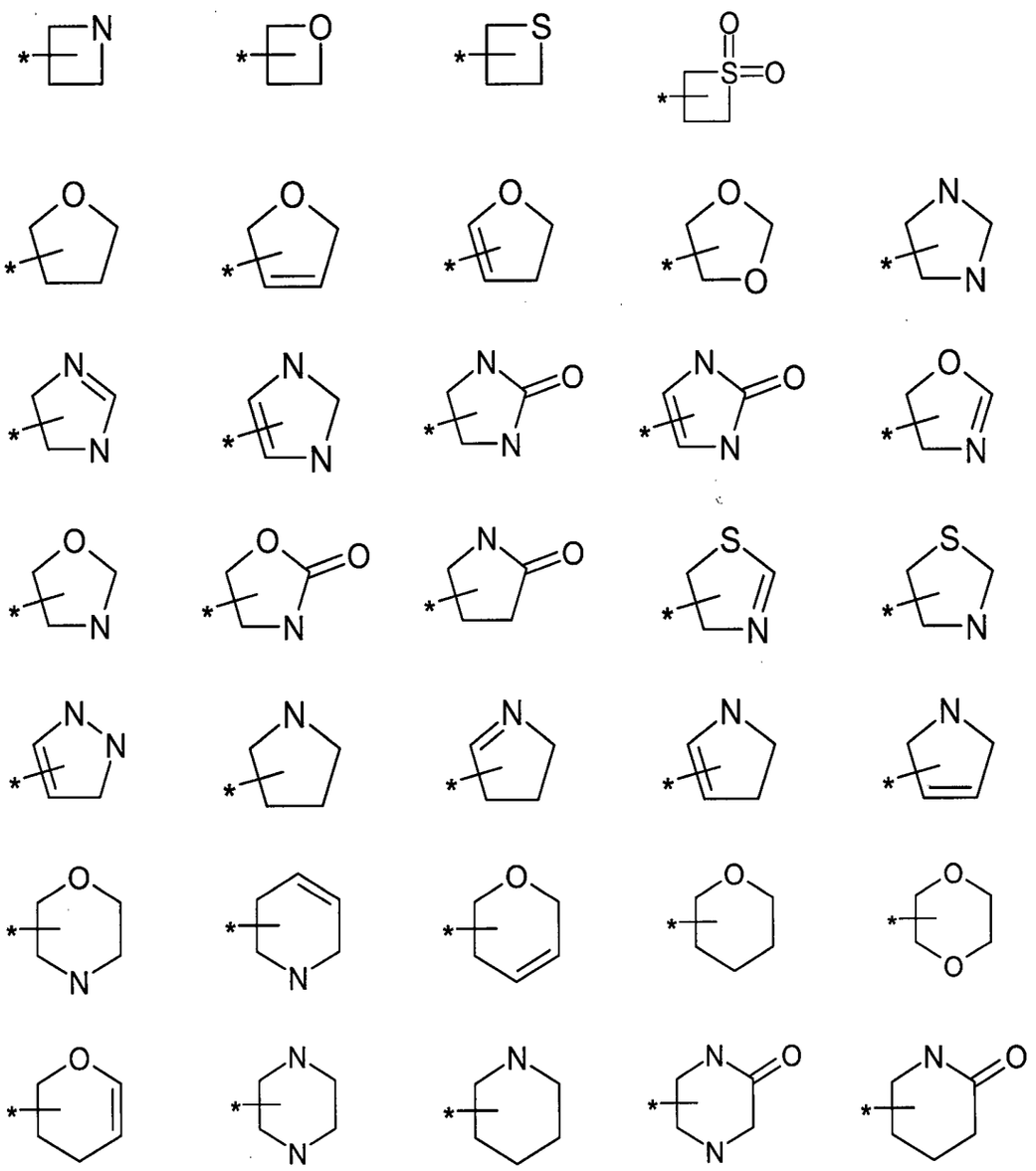
en la que

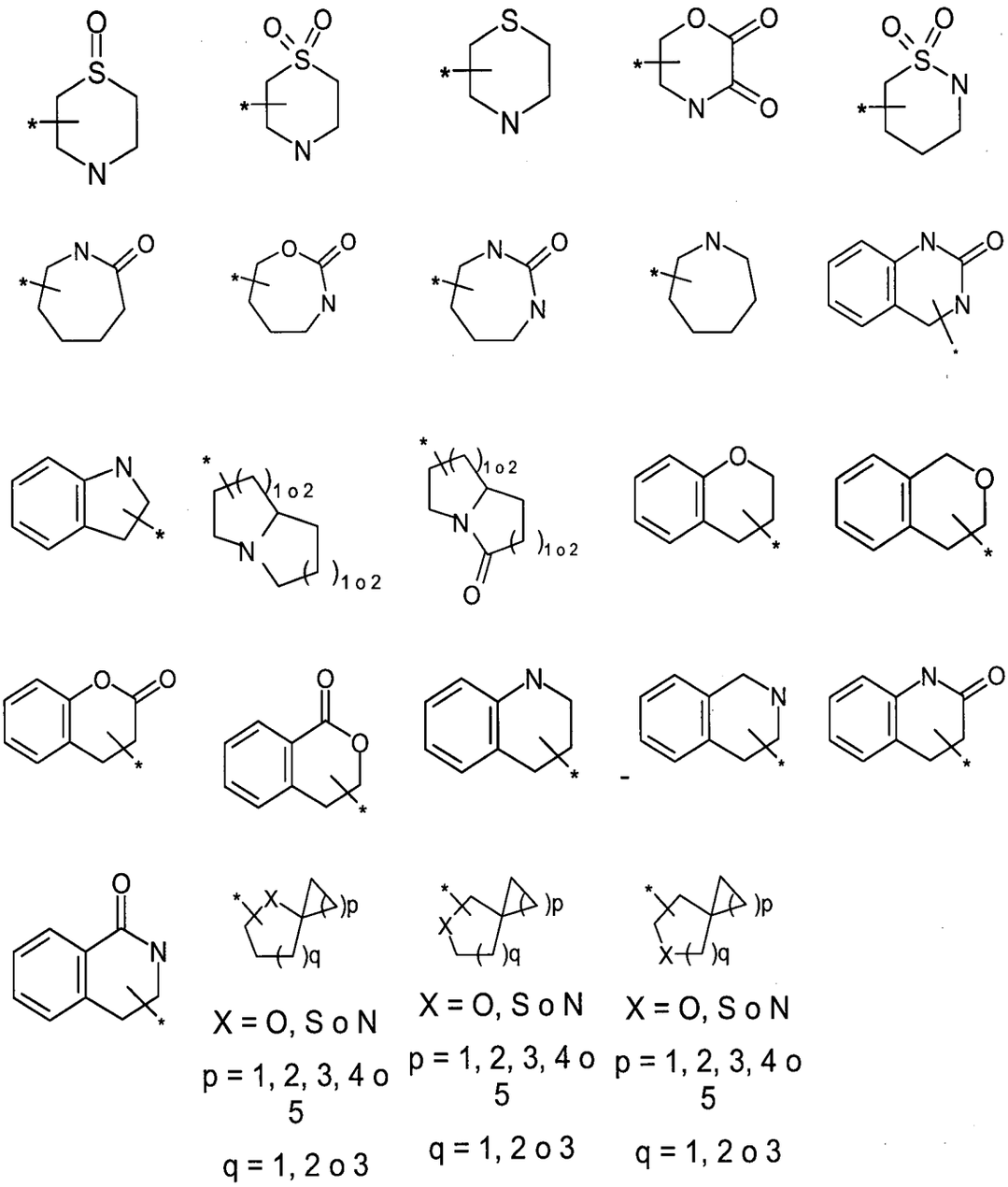
A, es el sistema de anillos de la fórmula I.1;

C es un segundo sistema de anillos de 3, 4, 5 o 6 miembros que está espiro-condensado con ***A*** y que aparte del átomo que comparte con ***A*** consiste solamente en átomos de carbono y que puede ser saturado o parcialmente saturado; los sustituyentes R^2 y/o R^3 independientemente uno de otro e independientemente de cada x e y, pueden estar en el anillo ***A*** o en el anillo ***C***.

Hc^3:

Hc es un grupo heterociclilo seleccionado del grupo de





X = O, S o N
p = 1, 2, 3, 4 o 5
q = 1, 2 o 3

X = O, S o N
p = 1, 2, 3, 4 o 5
q = 1, 2 o 3

X = O, S o N
p = 1, 2, 3, 4 o 5
q = 1, 2 o 3

Hc^4:

Hc es el grupo heterociclilo según la fórmula I.1 como se ha definido antes para **Hc^2**.

Hc^5:

Hc es el grupo heterociclilo según la fórmula I.2 como se ha definido antes para **Hc^2**.

Hc^6:

Hc es el grupo heterociclilo según la fórmula I.3 como se ha definido antes para Hc^2.

$Hc^{7.0}$:

Hc es un grupo heterocíclico monocíclico, no aromático, saturado, de 4 a 8, preferiblemente 5, 6 o 7 átomos en el anillo, en el que dichos átomos del anillo son átomos de carbono y 1, 2 o 3 heteroátomos, preferiblemente 1 heteroátomo, siendo seleccionados los heteroátomos entre oxígeno, nitrógeno y azufre, estando el azufre en la forma de $-S(O)_r-$ siendo r 0, 1 o 2, preferiblemente siendo r 0 y en el que preferiblemente dicho grupo heterocíclico está unido a la estructura química (scaffold) mediante un átomo de carbono del anillo que no está unido directamente a dicho heteroátomo del anillo.

$Hc^{7.1}$:

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo y piperazinilo, en el que preferiblemente el tetrahidropiranilo es 3- o 4-tetrahidropiranilo, el tetrahidrofuranilo es 3-tetrahidrofuranilo, y el piperidinilo es 3- o 4-piperidinilo.

Hc^8:

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo y pirrolidinilo, en el que preferiblemente el tetrahidropiranilo es 3- o 4-tetrahidropiranilo, el tetrahidrofuranilo es 3-tetrahidrofuranilo, y el piperidinilo es 3- o 4-piperidinilo.

Hc^9:

Hc se selecciona del grupo de piperidinilo y pirrolidinilo, preferiblemente 3- o 4-piperidinilo y 3- pirrolidinilo.

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Hc^{10}:

Hc se selecciona del grupo de tetrahidropiranilo y tetrahidrofuranilo, preferiblemente 3- o 4-tetrahidropiranilo y 3-tetrahidrofuranilo.

El sustituyente R^1 se define por las siguientes definiciones $R^{1.0.j}$, respectivamente de $R^{1.j}$, en las que el índice j describe el orden de preferencia, ascendiendo desde $R^{1.0.1}$ a definiciones más preferidas como $R^{1.0.2}$, y así sucesivamente a $R^{1.1}$, a $R^{1.2}$ y así sucesivamente:

$R^{1.0.1}$:

R^1 se selecciona del grupo de

alquil C_{1-8}-, alquenil C_{2-8}-, alquinil C_{2-8}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, aril-alquenil C_{2-6}-, aril-alquinil C_{2-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-alquenil C_{2-6}-, y heteroaril-alquinil C_{2-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-6}-O-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-O-, heteroaril-alquil C_{1-6}-O-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, piridin-2-ona-alquil C_{1-6}-O- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-O- estando el heterocicloalquilo C_{3-7} unido al O mediante uno de sus átomos

C del anillo, heterocicloalquil C_{3-7}-alquil C_{1-6}-O- estando el heterocicloalquilo C_{3-7} unido al alquil C_{1-6}- mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, $R^{10}O$-CO-O-, $R^{10}O$-CO-O-alquil C_{1-6}-, $R^{10}O$-CO-$(R^{10})N$-, $R^{10}O$-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y/o alquil C_{1-6}-SO_2-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, $R^{10}O$-CO-O-, $R^{10}O$-CO-O-alquil C_{1-6}-, $R^{10}O$-CO-$(R^{10})N$-, $R^{10}O$-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-$(R^{10})N$-, $(R^{10})_2N$-SO_2-$(R^{10})N$-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y/o alquil C_{1-6}-SO_2-.

$R^{1.0.2}$.

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo y heteroaril-alquil C_{1-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-alquil C_{1-6}-, R^{10}O-CO-O-, y/o R^{10}O-CO-(R^{10})N-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo-, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, bencil-O-, y/o $(R^{10})_2N$-CO-, donde el piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-.

$R^{1.0.3}$.

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, pirimidinilo, pirazolilo, tiazolilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-3}-O-, CF_3O-, CF_3-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, HO-alquil C_{1-6}-, oxadiazolilo, oxazolilo, isoxazolilo, triazolilo, tiazolilo, pirrolilo, furanilo, pirazolilo, piridilo, piridazinilo, pirimidinilo, $(R^{10})_2N$-CO-alquil C_{1-6}-, $(R^{10})_2N$-CO- y/o fenilo,

donde los grupos oxadiazolilo, oxazolilo, isoxazolilo, triazolilo, tiazolilo, pirrolilo, furanilo, pirazolilo, piridilo, piridazinilo, pirimidinilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CF_3-, CH_3O-, CF_3O-, H_2NCO-, NC-, morfolinilo y/o bencil-O-.

$R^{1.0.4.}$:

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etilo, 1- y 2-propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3-, oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo, y/o fenilo,

donde los grupos oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CH_3O-, H_2NCO- y/o NC-.

$R^{1.1.}$:

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R^1 se selecciona del grupo de

alquil C_{1-8}-, alquenil C_{2-8}-, alquinil C_{2-8}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, y heteroaril-alquil C_{1-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-6}-O-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-O-, heteroaril-alquil C_{1-6}-O-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-O- estando el heterocicloalquilo C_{3-7} unido al O mediante uno de sus átomos C del anillo, heterocicloalquil C_{3-7}-alquil C_{1-6}-O- estando el heterocicloalquilo C_{3-7} unido al alquil C_{1-6}- mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-$(R^{10})N$-, R^{10}O-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y alquil C_{1-6}-SO_2-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo mencionados antes pueden estar opcionalmente sustituidos con HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-}

$_{6}$-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-alquil C_{1-6}-, $(R^{10})_2$N-CO-O-, $(R^{10})_2$N-CO-(R^{10})N-, $(R^{10})_2$N-SO_2-(R^{10})N-, $(R^{10})_2$N-CO-O-alquil C_{1-6}-, $(R^{10})_2$N-CO-(R^{10})N-alquil C_{1-6}-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-alquil C_{1-6}-, $(R^{10})_2$N-SO_2-(R^{10})N-alquil C_{1-6}-, $(R^{10})_2$N-SO_2-, $(R^{10})_2$N-SO_2-alquil C_{1-6}-, o alquil C_{1-6}-SO_2-.

$R^{1.2.}$:

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, arilo y heteroarilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2$N-, $(R^{10})_2$N-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2$N-CO-, $(R^{10})_2$N-CO-alquil C_{1-6}-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-alquil C_{1-6}-, R^{10}O-CO-O-, y R^{10}O-CO-(R^{10})N-;

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo mencionados antes pueden estar opcionalmente sustituidos con NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, o $(R^{10})_2$N-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-.

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$R^{1.3}$:

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, pirimidinilo, pirazolilo, tiazolilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados del grupo que consiste en HO-, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-3}-O-, CF_3O-, CF_3-, flúor, cloro, bromo, heterocicloalquil C_{3-7}- y heterocicloalquil C_{3-7}-alquil C_{1-6}-.

$R^{1.4}$:

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados del grupo que consiste en NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3- y halógeno (siendo seleccionado preferiblemente el halógeno del grupo de flúor, cloro, y bromo).

El sustituyente opcional R^2 se define por las siguientes definiciones $R^{2.0.k}$, respectivamente de $R^{2.k}$, donde el índice k describe el orden de preferencia, ascendiendo desde $R^{2.0.1}$ hasta definiciones más preferidas (como $R^{2.2}$), y así sucesivamente:

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$R^{2.0.1.}$:

R^2 independientemente de cualquier otro R^2 se selecciona del grupo de

H-, flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxi-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, preferiblemente alquil C_{1-6}-S-alquil C_{2-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, aril-alquenil C_{2-6}-, aril-alquinil C_{2-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-alquenil C_{2-6}-, heteroaril-alquinil C_{2-6}-, R^{10}-O-alquil C_{2-3}-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-(R^{10})N-, R^{10}-CO-, $(R^{10})_2N$-CO-(R^{10})N-, R^{10}-O-CO-(R^{10})N-, R^{10}-SO_2-(R^{10})N-, alquil C_{1-6}-SO_2- y oxo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en
flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, alquil C_{1-6}-O-, alquil C_{1-6}-O-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-,

y en el caso en que R^2 está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 debe ser independientemente de cualquier otro R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-,

arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en

flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-.

$R^{2.1}$:

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxi-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{2-3}-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-, y alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en

flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, alquil C_{1-6}-O-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-,

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***,

este **R^2** será independientemente de cualquier otro R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-.

$R^{2.2}$:

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), $(R^{10})_2N$-CO- y R^{10}-CO-$(R^{10})N$-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, alquil C_{1-6}-O-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-,

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y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este **R^2** será independientemente de cualquier otro R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, R^{10}O-CO-, $(R^{10})_2$N-CO-, R^{10}-CO-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2$N-, $(R^{10})_2$N-alquil C_{1-3}-, y $(R^{10})_2$N-CO-.

$R^{2.3}$:

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), $(R^{10})_2$N-CO- y R^{10}-CO-(R^{10})N-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo y alquil C_{1-6}-,

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este **R^2** será independientemente de cualquier otro **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, R^{10}O-CO-, $(R^{10})_2$N-CO-, R^{10}-CO-, o alquil C_{1-6}-SO_2-,

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donde estos sustituyentes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor y alquil C_{1-6}-.

$R^{2.4}$:

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H- y alquil C_{1-6}- (preferiblemente alquilo C_{2-6}),

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, entonces **R^2** será independientemente de cualquier otro **R^2**: H-, alquil C_{1-6}-, R^{10}O-CO-, $(R^{10})_2$N-CO-, R^{10}-CO-, fenil-CO- y fenil-O-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor y alquil C_{1-6}-.

$R^{2.5}$:

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2 H-, alquil C1-6-CO-, alquil C1-6-O-CO-, alquil C1-6-, fenil-CO-, fenil-O-CO-, (alquil C1-6)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor.

El sustituyente opcional $\mathbf{R^3}$ se define por las siguientes definiciones $\mathbf{R^{3.ł}}$ donde el índice ł describe el orden de preferencia, ascendiendo desde (esto es, $\mathbf{R^{3.1}}$) a preferiblemente (esto es, $\mathbf{R^{3.2}}$), y así sucesivamente:

$\mathbf{R^{3.1}}$:

$\mathbf{R^3}$ se selecciona del grupo de H-, hidroxi y R^{10}-O-.

$\mathbf{R^{3.2}}$:

$\mathbf{R^3}$ se selecciona del grupo de H-, hidroxilo y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-.

$\mathbf{R^{3.3}}$:

$\mathbf{R^3}$ es H.

Los sustituyentes $\mathbf{R^4}$ y $\mathbf{R^5}$ se definen por las siguientes definiciones $\mathbf{R^{4/5.m}}$ donde el índice m describe el orden de preferencia, ascendiendo desde (esto es, $\mathbf{R^{4/5.1}}$) a preferiblemente (esto es, $\mathbf{R^{4/5.2}}$), y así sucesivamente:

$\mathbf{R^{4/5.1}}$:

$\mathbf{R^4}$ y $\mathbf{R^5}$ independientemente uno de otro se seleccionan del grupo de H-, flúor, F_3C-, HF_2C-, FH_2C-, y alquil C_{1-3}-,

o

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R^4 y R^5 junto con el átomo de carbono al que están unidos forman un grupo cicloalquilo de 3 a 6 miembros,

donde los miembros mencionados antes incluyendo el anillo carbocíclico formado, pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil.C_{1-6}-, alquil C_{1-6}-O- y (alquil C_{1-6}-)$_2$N-CO-.

$R^{4/5.2.}$:

R^4 y R^5 independientemente uno de otro, se seleccionan del grupo de H-, flúor y metilo.

$R^{4/5.3.}$:

R^4 y R^5 both son H-.

El sustituyente R^{10} se define por las siguientes definiciones $R^{10.0.n}$, respectivamente de $R^{10.n}$, donde el índice n describe el orden de preferencia. La preferencia asciende desde $R^{10.0.1}$ a preferiblemente $R^{10.0.2}$, y así sucesivamente hasta $R^{10.4}$:

$R^{10.0.1.}$:

R^{10} independientemente de cualquier otro R^{10} se selecciona del grupo de

H- (pero no en el caso en que es parte de un grupo se selecciona entre R^{10}O-CO-, R^{10}-SO_2- o R^{10}-CO-), F_3C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-3}-, heteroarilo, y heteroaril-alquil C_{1-3}-,

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y en el caso en que dos grupos $\mathbf{R^{10}}$ estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y en el que uno de los grupos $-CH_2-$ del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -S-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})- preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2N-CO-$, estos dos $\mathbf{R^{10}}$ junto con dicho átomo de nitrógeno se unen para formar un grupo seleccionado del grupo de piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,

y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}- y alquil C_{1-6}-O-.

$R^{10.0.2.}$:

$\mathbf{R^{10}}$ independientemente de cualquier otro $\mathbf{R^{10}}$ se selecciona del grupo de H- (pero no en el caso en que es parte de un grupo seleccionado entre $R^{10}O-CO-$, $R^{10}-SO_2-$ o $R^{10}-CO-$), alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, arilo y heteroarilo,

y en el caso en que dos grupos R10 estén ambos unidos al mismo átomo de nitrógeno pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos -CH2- del anillo heterocicloalquilo formado puede estar reemplazado por -O-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})-
y preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2N-CO-$, estos dos $\mathbf{R^{10}}$ junto con dicho átomo de nitrógeno se unen para formar un

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grupo seleccionado del grupo de piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,

y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-.

$R^{10.0.3}$:

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

H- (pero no en el caso en que es parte de un grupo que se selecciona entre R^{10}O-CO-, R^{10}-SO_2- o R^{10}-CO-), alquil C_{1-6}-, cicloalquil C_{3-7}-, arilo y heteroarilo, preferiblemente el arilo es fenilo y también preferiblemente heteroarilo se selecciona del grupo de oxadiazolilo, oxazolilo, isoxazolilo, triazolilo, tiazolilo, pirrolilo, furanilo, pirazolilo, piridilo, piridazinilo, y pirimidinilo;

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-.

$R^{10.0.4}$:

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de alquil C_{1-6}-, fenilo y piridilo y en el caso en que **R^{10}** es un sustituyente de un átomo de nitrógeno **R^{10}** se selecciona del grupo de H, alquil C_{1-6}-, fenilo y piridilo;

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-.

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$R^{10.0.5}$:

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de metil-, etil- y *terc*-butilo, y en el caso en que **R^{10}** es un sustituyente de un átomo de nitrógeno **R^{10}** se selecciona del grupo de H, metil-, etil- y *terc*-butilo;

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más átomos de flúor.

$R^{10.1}$:

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de H- (pero no en el caso en que es parte de un grupo que se selecciona entre $R^{10}O$-CO-, R^{10}-SO_2- o R^{10}-CO-), F_3C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, arilo, aril-alquil C_{1-3}-, heteroarilo, y heteroaril-alquil C_{1-3}-,

y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos -CH_2- del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -S-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})- preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2$N-CO-, estos dos grupos R^{10} junto con dicho átomo de nitrógeno se unen para formar un grupo seleccionado entre piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,

y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-,

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F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}- y alquil C_{1-6}-O-.

$R^{10.2}$:

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

alquil C_{1-6}-, cicloalquil C_{3-7}-, arilo y heteroarilo,

y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos -CH_2- del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})- preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2$N-CO-, estos dos grupos R^{10} junto con dicho nitrógeno se unen para formar un grupo seleccionado entre piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,
y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-.

$R^{10.3}$:

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

alquil C_{1-6}-, cicloalquil C_{3-7}-, arilo y heteroarilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes

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seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-.

$R^{10.4}$:

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de alquil C_{1-6}-, fenilo y piridilo

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-.

x = 0, 1, 2, 3 o 4, preferiblemente x = 0, 1 o 2, más preferiblemente x = 0, 1 y más preferiblemente x = 0; si no se especifica otra cosa en el contexto;

y = 0, o 1, preferiblemente y = 0, si no se especifica otra cosa en el contexto;

con la condición de que para cada realización aplicable de la fórmula I de la invención - tal como por ejemplo las realizaciones que comprenden ***Hc***^{1} y ***Hc***^{3},

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador -CH_2-.

Los valores de x e y son independientes uno de otro.

Los símbolos de índice i, j, k, ł, m, n en $R^{1.j}$, $R^{2.k}$ etc. son índices, cada uno de los cuales tendrá el significado de un número entero: 1, 2, 3, etc. de forma que cada $R^{1.j}$, $R^{2.k}$ etc. representa una realización individual caracterizada, de los correspondientes sustituyentes para los cuales $R^{1.j}$, $R^{2.k}$ etc. son las definiciones.

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Así dadas las definiciones anteriores, un prototipo genérico de los compuestos según la fórmula I se caracteriza completamente por el término ($\underline{Hc}^{i}$ $R^{1.j}$ $R^{2.k}$ $R^{3.ł}$ $R^{4/5.m}$ $R^{10.n}$) si para cada letra i, j, k, ł, m y n se da un número individual donde – si no se indica otra cosa en un contexto específico - para cada una de tales realizaciones ($\underline{Hc}^{i}$ $R^{1.j}$ $R^{2.k}$ $R^{3.ł}$ $R^{4/5.m}$ $R^{10.n}$) **x** será 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2 e **y** será 0 o 1 y con la condición de que para cada realización aplicable de la fórmula I de la invención, si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un grupo $-CH_2-$.

En otras palabras, cada realización ($\underline{Hc}^{i}$ $R^{1.j}$ $R^{2.k}$ $R^{3.ł}$ $R^{4/5.m}$ $R^{10.n}$) representa un prototipo o subconjunto de prototipos completamente caracterizado según la fórmula general I, esto es, un prototipo genérico de compuestos que es objeto de la presente invención.

Dicha realización define las variables ***Hc***, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$ y si es aplicable $\mathbf{R^{10}}$ de la fórmula I y en las que – si no se indica otra cosa en un contexto específico - **x** será 0, 1, 2, 3 o 4, siendo preferiblemente 0, 1 o 2 e **y** será 0 o 1 y con la condición de que para cada realización aplicable de la fórmula I de la invención, si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un grupo $-CH_2-$.

En un **1er aspecto general** de la presente invención, el compuesto o compuestos de la presente invención se definen por la siguiente realización según la fórmula general I caracterizada por

$\underline{Hc}^{1}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$

en la que

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2

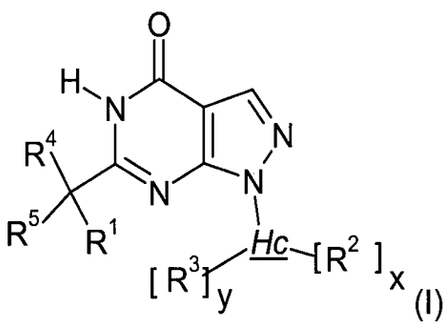
y independientemente de cualquier x: **y** = 0 o 1,

y sus sales y/o solvatos y/o tautómeros etc. farmacéuticamente aceptables;

con la condición de que

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador $-CH_2-$.

Según lo anterior, esto significa que el 1er aspecto de la presente invención se refiere a compuestos según la fórmula general I



(I)

en la que

Hc es como se define para **Hc**^{1};

R^{1} es como se define para **R**$^{1.0.1}$;

R^{2} es como se define para **R**$^{2.0.1}$;

R^{3} es como se define para **R**$^{3.1}$;

R^{4} y **R**$^{4/}$ son como se define para **R**$^{4/5.1}$;

R^{10} es como se define para **R**$^{10.0.1}$;

x independientemente de cualquier y: **x** es 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2;

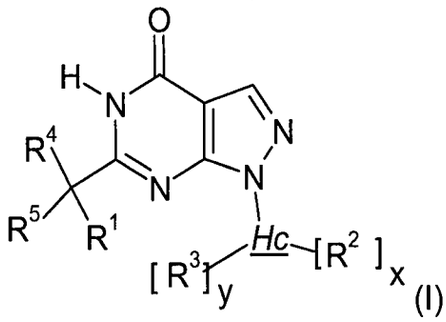
y independientemente de cualquier x: **y** = 0 o 1;

y sus sales y/o solvatos y/o tautómeros etc. farmacéuticamente aceptables;

con la condición de que

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador $-CH_2-$.

Por tanto este **1er aspecto** de la invención se define como un compuesto según la fórmula general I



(I)

en la que

Hc es un grupo heterociclilo mono-, bi- o tricíclico, cuyos miembros del anillo son átomos de carbono y al menos 1, preferiblemente 1, 2 o 3, heteroátomos, que se seleccionan del grupo de nitrógeno, oxígeno y azufre, que está en la forma de $-S(O)_r-$ siendo r 0, 1 o 2, y

- dicho grupo heterociclilo es o comprende 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo y
- dicho grupo heterociclilo está unido a la estructura química (scaffold) por dicho 1 anillo monocíclico saturado, o parcialmente

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insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo;

R^1 se selecciona del grupo de

alquil C_{1-8}-, alquenil C_{2-8}-, alquinil C_{2-8}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, aril-alquenil C_{2-6}-, aril-alquinil C_{2-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-alquenil C_{2-6}-, y heteroaril-alquinil C_{2-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-6}-O-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-O-, heteroaril-alquil C_{1-6}-O-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, piridin-2-ona-alquil C_{1-6}-O- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-O- estando el heterocicloalquilo C_{3-7} unido al O mediante uno de sus átomos C del anillo, heterocicloalquil C_{3-7}-alquil C_{1-6}-O- estando el heterocicloalquilo C_{3-7} unido al alquil C_{1-6}- mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, $R^{10}O$-CO-O-, $R^{10}O$-CO-O-alquil C_{1-6}-, $R^{10}O$-CO-$(R^{10})N$-, $R^{10}O$-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y/o alquil C_{1-6}-SO_2-,

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donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-$(R^{10})N$-, R^{10}O-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-$(R^{10})N$-, $(R^{10})_2N$-SO_2-$(R^{10})N$-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y/o alquil C_{1-6}-SO_2-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de:

H-, flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxi-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, preferiblemente alquil C_{1-6}-S-alquil C_{2-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, aril-alquenil C_{2-6}-, aril-alquinil C_{2-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-alquenil C_{2-6}-, heteroaril-alquinil C_{2-6}-, R^{10}-O-alquil C_{2-3}-, $(R^{10})_2N$-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, R^{10}-O-CO-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-, alquil C_{1-6}-SO_2- y oxo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-,

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HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, alquil C_{1-6}-O-, alquil C_{1-6}-O-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-,

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-;

R^3 se selecciona del grupo de

H-, hidroxi y R^{10}-O-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, F_3C-, HF_2C-, FH_2C-, y alquil C_{1-3}-,

o

R^4 y **R^5** junto con el átomo de carbono al que están unidos forman un grupo cicloalquilo de 3 a 6 miembros,

donde los miembros mencionados antes incluyendo el anillo carbocíclico formado, pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en

flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, alquil C_{1-6}-O- y (alquil C_{1-6}-)$_2$N-CO-;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

H- (pero no en el caso en que es parte de un grupo que se selecciona entre R^{10}O-CO-, R^{10}-SO_2- o R^{10}-CO-), F_3C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-3}-, heteroarilo, y heteroaril-alquil C_{1-3}-,

y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos -CH_2- del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -S-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})-, preferiblemente, y en particular preferiblemente en el caso de (R^{10})$_2$N-CO-, estos dos R^{10} junto con dicho átomo de nitrógeno se unen para formar un grupo seleccionado del grupo de piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,

y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}- y alquil C_{1-6}-O-;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

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y sus sales farmacéuticamente aceptables,

con la condición de que para cada realización aplicable de la fórmula I de la invención,

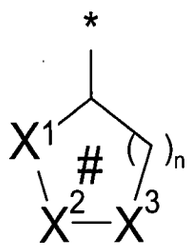
si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador $-CH_2-$.

*Esto significa que ningún sustituyente comprende un grupo CH_2- mediante el cual se une al oxetanilo.

Un **2° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc es un grupo heterociclilo según una fórmula que se selecciona del grupo de fórmulas I.1, I.2 y I.3:

fórmula I.1:



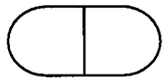
en la que

n = 1, 2, 3;

X^1, X^2, X^3, independientemente uno de otro, son CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, o $S(O)_r$ siendo r = 0, 1, 2, donde al menos uno de X^1, X^2, X^3 es O, NH, NR^2 o $S(O)_r$.;

#: significa que el anillo no es aromático y cuando n = 1, un enlace dentro del sistema de anillos puede ser opcionalmente un doble enlace y cuando n = 2 o n = 3 un enlace o dos enlaces dentro del sistema de anillos pueden ser opcionalmente dobles enlaces, con los que se reemplazan los átomos de hidrógeno unidos a los miembros del anillo, donde tales dobles enlaces son preferiblemente un doble enlace C-C, y el anillo es más preferiblemente saturado;

fórmula I.2:



A ***B***

en la que

A es el sistema de anillos de la fórmula I.1;

B es un segundo sistema de anillos de 3, 4, 5 o 6 miembros que está anillado con ***A*** y que aparte de los dos átomos y un enlace - que puede ser un enlace sencillo o doble - que comparte con ***A*** consiste solamente en átomos de carbono y que puede ser saturado, parcialmente saturado o aromático; los sustituyentes R^2 y/o R^3 independientemente uno de otro e independientemente de cada x o y pueden estar en el anillo ***A*** o en el anillo ***B***; donde los dos átomos del anillo que son compartidos por los dos sistema de anillos ***A*** y ***B*** pueden ser ambos átomos de carbono, pueden ser ambos átomos de nitrógeno o uno puede ser un átomo de carbono y el otro puede ser un átomo de nitrógeno, donde son preferidos dos átomos de carbono o un átomo de carbono y un átomo de nitrógeno y son más preferidos dos átomos de carbono;

fórmula I.3:

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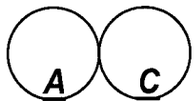

en la que

A, es el sistema de anillos de la fórmula I.1;

C es un segundo sistema de anillos, saturado o parcialmente saturado, de 3, 4, 5 o 6 miembros que está espiro-condensado con ***A*** y que aparte del átomo que comparte con ***A*** consiste solamente en átomos de carbono y los sustituyentes R^2 y/o R^3 independientemente uno de otro e independientemente de cada x e y pueden estar en el anillo ***A*** o en el anillo ***C***;

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo y heteroaril-alquil C_{1-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-,

$(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, $R^{10}O$-CO-O-, y/o $R^{10}O$-CO-$(R^{10})N$-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo-, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, bencil-O-, y/o $(R^{10})_2N$-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), $(R^{10})_2N$-CO- y R^{10}-CO-$(R^{10})N$-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo y alquil C_{1-6}-,

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor y alquil C_{1-6}-;

R^3 se selecciona del grupo de

H-, hidroxi, alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

H- (pero no en el caso en que es parte de un grupo que se selecciona entre R^{10}O-CO- o R^{10}-CO-), alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, arilo y heteroarilo,

y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos -CH_2- del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})-, preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2$N-CO-, estos dos R^{10} junto con dicho átomo de nitrógeno se unen para formar un grupo seleccionado del grupo de piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,

y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

Un **3er aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc es un grupo heterocíclico monocíclico, no aromático, saturado, de 4 a 8, preferiblemente 5, 6 o 7 átomos en el anillo, donde dichos átomos del anillo son átomos de carbono y 1, 2 o 3 heteroátomos, preferiblemente 1 heteroátomo, los heteroátomos se seleccionan entre oxígeno, nitrógeno y azufre, estando el azufre en la forma de – $S(O)_r$ - siendo r 0, 1 o 2, preferiblemente siendo r 0 y donde preferiblemente dicho grupo heterocíclico está unido a la estructura química (scaffold) mediante un átomo de carbono del anillo que no está unido directamente al heteroátomo del anillo;

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo y heteroaril-alquil C_{1-6}-,

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donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, $R^{10}O$-CO-O-, y/o $R^{10}O$-CO-$(R^{10})N$-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo-, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, bencil-O-, y/o $(R^{10})_2N$-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro **R^2**: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxi y C_{1-6}-alquil-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente siendo ambos H;

R^{10} independientemente de cualquier otro **R^{10}** seleccionado del grupo de alquil C_{1-6}-, fenilo y piridilo y en el caso en que **R^{10}** es un sustituyente de un átomo de nitrógeno **R^{10}** se selecciona del grupo de H, alquil C_{1-6}-, fenilo y piridilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables,

con la condición de que

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un grupo $-CH_2-$*.

*Esto significa que ningún sustituyente comprende un grupo CH_2- mediante el cual se une al oxetanilo.

Un **4° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo y piperazinilo, donde preferiblemente el tetrahidropiranilo es 3- o 4-tetrahidropiranilo, el tetrahidrofuranilo es 3-tetrahidrofuranilo, y el piperidinilo es 3- o 4-piperidinilo; más preferiblemente ***Hc*** es tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo, y de ellos preferiblemente, 3- y 4-tetrahidropiranilo, 3- y 4-piperidinilo y 3- pirrolidinilo;

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo y heteroaril-alquil C_{1-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, heterocicloalquil C_{3-7}-,

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heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, $R^{10}O$-CO-O-, y/o $R^{10}O$-CO-$(R^{10})N$-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo-, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, bencil-O-, y/o $(R^{10})_2N$-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

R^2 independientemente de cualquier otro **R^2** potencial se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que R^2 está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de alquil C_{1-6}-, fenilo y piridilo y en el caso en que **R^{10}** es un sustituyente de un átomo de nitrógeno **R^{10}** se selecciona del grupo de H, alquil C_{1-6}-, fenilo y piridilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

Un **5° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo y piperazinilo, donde preferiblemente el tetrahidropiranilo es 3- o 4-tetrahidropiranilo, el tetrahidrofuranilo es 3-tetrahidrofuranilo, y el piperidinilo es

3- o 4-piperidinilo; más preferiblemente ***Hc*** es tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo, y de ellos preferiblemente, 3- y 4-tetrahidropiranilo, 3- y 4-piperidinilo y 3- pirrolidinilo;

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, pirimidinilo, pirazolilo, tiazolilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-3}-O-, CF_3O-, CF_3-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, HO-alquil C_{1-6}-, oxadiazolilo, oxazolilo, isoxazolilo, triazolilo, tiazolilo, pirrolilo, furanilo, pirazolilo, piridilo, piridazinilo, pirimidinilo, $(R^{10})_2$N-CO-alquil C_{1-6}-, $(R^{10})_2$N-CO- y/o fenilo,

donde los grupos oxadiazolilo, oxazolilo, isoxazolilo, triazolilo, tiazolilo, pirrolilo, furanilo, pirazolilo, piridilo, piridazinilo, pirimidinilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CF_3-, CH_3O-, CF_3O-, H_2NCO-, NC-, morfolinilo y/o bencil-O-;

R^2 independientemente de cualquier otro **R^2** potencial se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que R^2 está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxilo y C_{1-6}-alquil-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de H, alquil C_{1-6}-, fenilo y piridilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cada uno de los otros **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cada uno de los otros **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

Un **6° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo, piperazinilo, preferiblemente tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo, y de ellos preferiblemente, 3- y 4-tetrahidropiranilo, 3- y 4-piperidinilo y 3- pirrolidinilo;

$\mathbf{R^1}$ se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etilo, 1- y 2-propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3-, oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo, y/o fenilo,

donde los grupos oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CH_3O-, H_2NCO- y/o NC-;

$\mathbf{R^2}$ independientemente de cualquier otro $\mathbf{R^2}$ se selecciona del grupo de H- o alquil C_{1-6}-,

y en los casos en que $\mathbf{R^2}$ está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

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donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

Un **7° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc se selecciona del grupo de piperidinilo y pirrolidinilo, preferiblemente 3- o 4-piperidinilo y 3- pirrolidinilo;

R^1 se selecciona del grupo de

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fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etilo, 1- y 2-propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3-, oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo, y/o fenilo,

donde los grupos oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CH_3O-, H_2NCO- y/o NC-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

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R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

Un **8° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc se selecciona del grupo de piperidinilo y pirrolidinilo, preferiblemente 3- o 4-piperidinilo y 3- pirrolidinilo;

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3- y halógeno, y el halógeno se selecciona preferiblemente entre flúor, cloro y bromo.

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R^2 independientemente de cualquier otro R^2 se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que R^2 está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^4 y **R^5** son ambos H

x = 0 o 1;

y = 0;

y sus sales farmacéuticamente aceptables.

Un **9° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc se selecciona del grupo de tetrahidropiranilo y tetrahidrofuranilo, preferiblemente 3- o 4-tetrahidropiranilo y 3-tetrahidrofuranilo.

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etilo, 1- y 2-propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

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donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3-, oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo, y/o fenilo,

donde los grupos oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CH_3O-, H_2NCO- y/o NC-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

donde los grupos alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, lo más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, lo más preferiblemente **y** = 0;

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y sus sales farmacéuticamente aceptables.

Un **10° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc se selecciona del grupo de tetrahidropiranilo y tetrahidrofuranilo, preferiblemente 3- o 4-tetrahidropiranilo y 3-tetrahidrofuranilo.

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3- y halógeno, y el halógeno se selecciona preferiblemente entre flúor, cloro y bromo.

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

donde los grupos alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, lo más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, lo más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

Un **11° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 1er aspecto de la invención, en el que

Hc se selecciona del grupo de tetrahidropiranilo y tetrahidrofuranilo, preferiblemente 3- o 4-tetrahidropiranilo y 3-tetrahidrofuranilo.

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3- y halógeno, y el halógeno se selecciona preferiblemente entre flúor, cloro y bromo.

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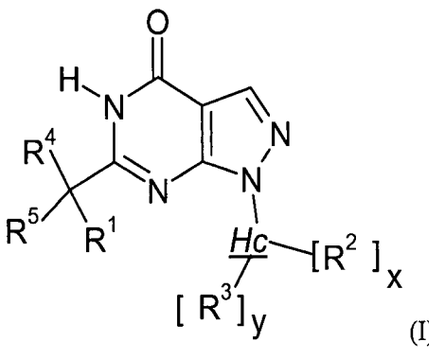
R^4 y R^5 son ambos H

x = 0;

y = 0;

y sus sales farmacéuticamente aceptables.

Un **12° aspecto** de la invención se refiere a un compuesto según la fórmula general I



(I),

en la que;

Hc es un grupo heterociclilo mono-, bi- o tricíclico, cuyos miembros del anillo son átomos de carbono y al menos 1, preferiblemente 1, 2 o 3, heteroátomos, que se seleccionan del grupo de nitrógeno, oxígeno y azufre, que está en la forma de $-S(O)_r$ - siendo r 0, 1 o 2, y

- dicho grupo heterociclilo es o comprende 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo y
- dicho grupo heterociclilo está unido a la estructura química (scaffold) por dicho 1 anillo monocíclico saturado, o parcialmente

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insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo.

R^1 se selecciona del grupo de

alquil C_{1-8}-, alquenil C_{2-8}-, alquinil C_{2-8}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, y heteroaril-alquil C_{1-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-6}-O-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-O-, heteroaril-alquil C_{1-6}-O-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-O- estando el heterocicloalquilo C_{3-7} unido al O mediante uno de sus átomos C del anillo, heterocicloalquil C_{3-7}-alquil C_{1-6}-O- estando el heterocicloalquilo C_{3-7} unido al alquil C_{1-6}- mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-$(R^{10})N$-, R^{10}O-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y alquil C_{1-6}-SO_2-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo mencionados antes pueden estar opcionalmente sustituidos preferiblemente independientemente uno de otro, con HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, $R^{10}O$-CO-O-, $R^{10}O$-CO-O-alquil C_{1-6}-, $R^{10}O$-CO-$(R^{10})N$-, $R^{10}O$-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-$(R^{10})N$-, $(R^{10})_2N$-SO_2-$(R^{10})N$-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y alquil C_{1-6}-SO_2-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxi-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{2-3}-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-, y alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, alquil C_{1-6}-O-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-,

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y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-;

R^3 se selecciona independientemente del grupo de H-, hidroxi y R^{10}-O-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, F_3C-, HF_2C-, FH_2C-, y alquil C_{1-3}-,

o

R^4 y R^5 junto con el átomo de carbono al que están unidos forman un grupo cicloalquilo de 3 a 6 miembros,

donde los miembros mencionados antes incluyendo el anillo carbocíclico formado, pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, alquil C_{1-6}-O- y (alquil C_{1-6}-)$_2$N-CO-;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

H- (pero no en el caso en que es parte de un grupo que se selecciona entre $R^{10}O$-CO-, R^{10}-SO_2- o R^{10}-CO-), F_3C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, arilo, aril-alquil C_{1-3}-, heteroarilo, y heteroaril-alquil C_{1-3}-,

y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos -CH_2- del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -S-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})- preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2$N-CO-, estos dos grupos R^{10} junto con dicho átomo de nitrógeno se unen para formar un grupo seleccionado entre piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,
y donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}- y alquil C_{1-6}-O-;

x independientemente de cada uno de los otros **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cada uno de los otros **y** = 0, o 1, más preferiblemente **y** = 0;

y sus formas salinas o solvatos farmacéuticamente aceptables,

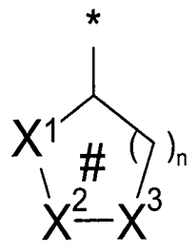
con la condición de que

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador $-CH_2-$.

Un **13° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 12° aspecto de la invención, en el que

Hc es un grupo heterociclilo según una fórmula que se selecciona del grupo de fórmulas I.1, I.2 y I.3:

fórmula I.1:



en la que

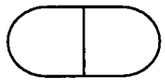
n = 1, 2, 3;

X^1, X^2, X^3, independientemente uno de otro, son CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, o $S(O)_r$ siendo r = 0, 1, 2, donde al menos uno de X^1, X^2, X^3 es O, NH, NR^2 o $S(O)_r$.;

#: significa que el anillo no es aromático y cuando n = 1, un enlace dentro del sistema de anillos puede ser opcionalmente un doble enlace y cuando n = 2 o n = 3 un enlace o dos enlaces dentro del sistema de anillos pueden ser opcionalmente dobles enlaces, con los que se reemplazan los átomos de

hidrógeno unidos a los miembros del anillo, donde tales dobles enlaces son preferiblemente un doble enlace C-C, y el anillo es más preferiblemente saturado;

fórmula I.2:



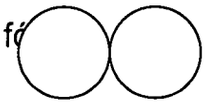
A ***B***

en la que

A es el sistema de anillos de la fórmula I.1;

B es un segundo sistema de anillos de 3, 4, 5 o 6 miembros que está anillado con ***A*** y que aparte de los dos átomos y un enlace - que puede ser un enlace sencillo o doble - que comparte con ***A*** consiste solamente en átomos de carbono y que puede ser saturado, parcialmente saturado o aromático; los sustituyentes R^2 y/o R^3 independientemente uno de otro, e independientemente de cada x o y pueden estar en el anillo ***A*** o en el anillo ***B***; donde los dos átomos del anillo que son compartidos por los dos sistema de anillos ***A*** y ***B*** pueden ser ambos átomos de carbono, pueden ser ambos átomos de nitrógeno o uno puede ser un átomo de carbono y el otro puede ser un átomo de nitrógeno, donde son preferidos dos átomos de carbono o un átomo de carbono y un átomo de nitrógeno y son más preferidos dos átomos de carbono;

fó



A ***C***

en la que

A, es el sistema de anillos de la fórmula I.1;

C es un segundo sistema de anillos, saturado o parcialmente saturado, de 3, 4, 5 o 6 miembros que está espiro-condensado con ***A*** y que aparte del átomo que comparte con ***A*** consiste solamente en átomos de carbono y los sustituyentes R^2 y/o R^3 independientemente uno de otro, e independientemente de cada x e y pueden estar en el anillo ***A*** o en el anillo ***C***;

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, arilo y heteroarilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, $R^{10}O$-CO-O-, y $R^{10}O$-CO-$(R^{10})N$-;

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo mencionados antes pueden estar opcionalmente sustituidos preferiblemente independientemente uno de otro, con NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, o $(R^{10})_2N$-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), $(R^{10})_2N$-CO-, R^{10}-CO-(R^{10})N-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo y alquil C_{1-6}-,

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor y alquil C_{1-6}-;

R^3 independientemente de cualquier otro **R^3** se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-; preferiblemente R^3 es H;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo; preferiblemente independientemente uno de otro, son H- o flúor, más preferiblemente **R^4** y **R^5** son H;

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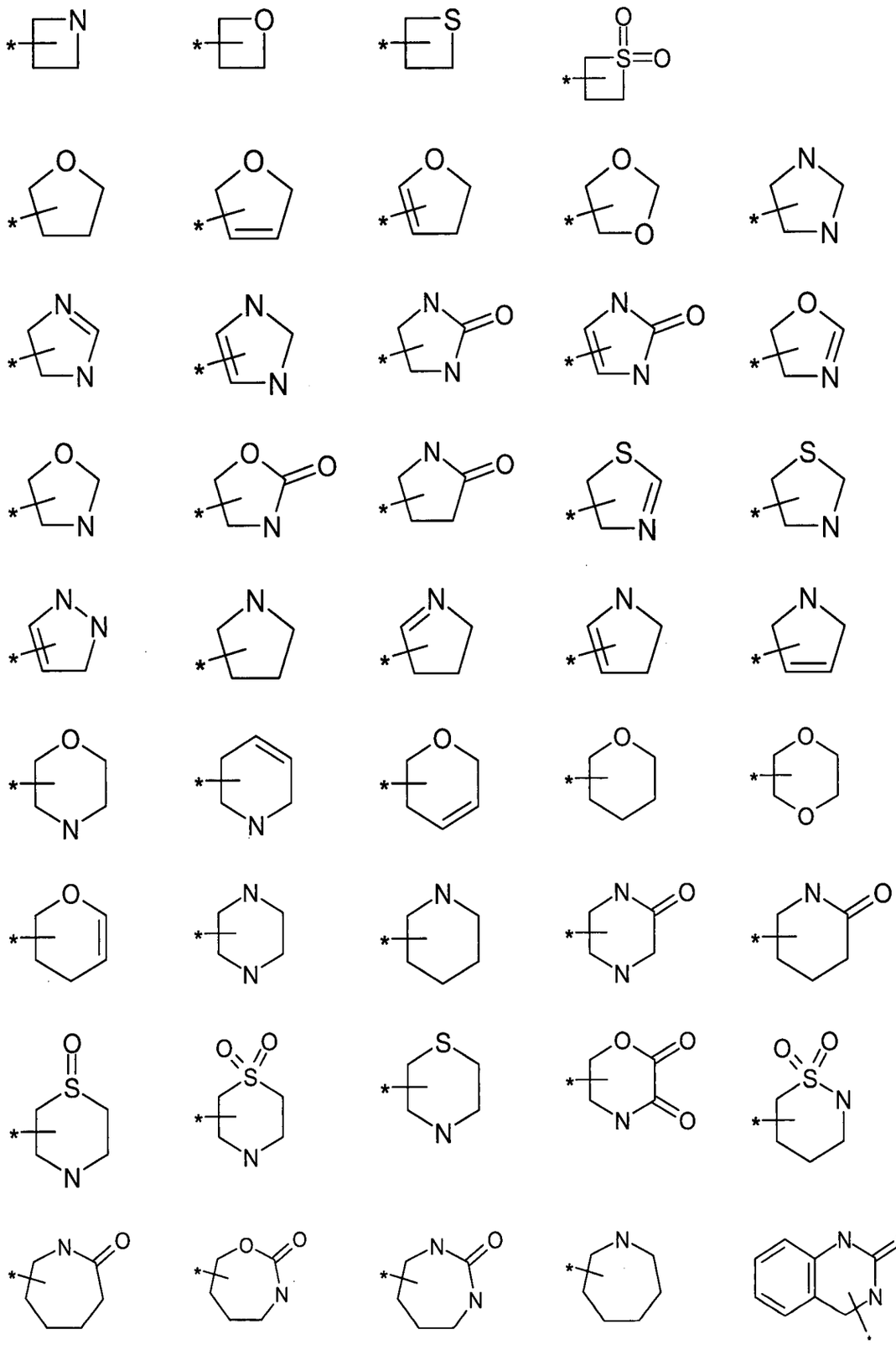
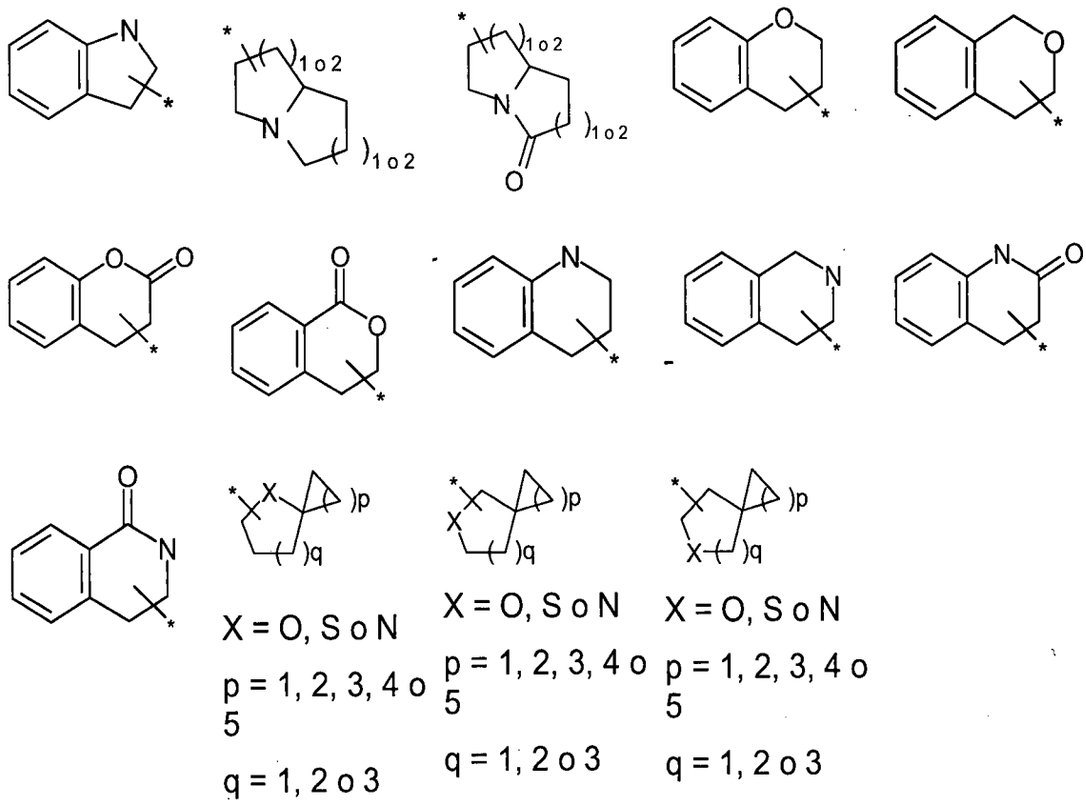
Un **14° aspecto** de la invención se refiere a un compuesto según la fórmula general I del 12° aspecto de la invención, en el que

Hc es un grupo heterociclilo seleccionado del grupo de





X = O, S o N
p = 1, 2, 3, 4 o 5
q = 1, 2 o 3

X = O, S o N
p = 1, 2, 3, 4 o 5
q = 1, 2 o 3

X = O, S o N
p = 1, 2, 3, 4 o 5
q = 1, 2 o 3

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, arilo y heteroarilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, $R^{10}O$-CO-O-, y $R^{10}O$-CO-$(R^{10})N$-;

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo mencionados antes pueden estar opcionalmente sustituidos preferiblemente independientemente uno de otro, con NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, o $(R^{10})_2$N-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), $(R^{10})_2$N-CO-, R^{10}-CO-(R^{10})N-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo y alquil C_{1-6}-,

y en los casos en que R^2 está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, R^{10}O-CO-, $(R^{10})_2$N-CO-, R^{10}-CO-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor y alquil C1-6-;

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R^3 independientemente de cualquier otro **R^3** se selecciona del grupo de

H-, hidroxilo y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo; preferiblemente independientemente uno de otro, se seleccionan del grupo de H- y flúor, más preferiblemente **R^4** y **R^5** son H;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

alquil C_{1-6}-, cicloalquil C_{3-7}-, arilo y heteroarilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cada uno de los otros **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cada uno de los otros **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales o solvatos farmacéuticamente aceptables

con la condición de que

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador $-CH_2-$.

Un **15° aspecto** de la invención se refiere a un compuesto según el 13° aspecto de la invención, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo;

y

$\mathbf{R^2}$ independientemente de cualquier otro $\mathbf{R^2}$ es H- o alquil C_{1-6}-,

y en los casos en que R^2 está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

y

R^4 y R^5 son H

y

$\mathbf{R^{10}}$ independientemente de cualquier otro $\mathbf{R^{10}}$ se selecciona del grupo de alquil C_{1-6}-, fenilo, y piridilo

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes

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seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-.

Un **16° aspecto** de la invención se refiere a un compuesto según el 15° aspecto de la invención, en el que

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, pirimidinilo, pirazolilo, tiazolilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1-and 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados del grupo que consiste en HO-, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-3}-O-, CF_3O-, CF_3-, flúor, cloro, bromo, heterocicloalquil C_{3-7}- y heterocicloalquil C_{3-7}-alquil C_{1-6}-.

Un **17° aspecto** de la invención se refiere a un compuesto con todas las características según el 16° aspecto de la invención, excepto en que

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados del grupo que consiste en NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3- y halógeno, y el halógeno se selecciona preferiblemente del grupo de flúor, cloro y bromo.

Un **aspecto específico** de la invención **(18° aspecto)** se refiere - independientemente uno de otro, y separable de ellos - a cada uno de los siguientes compuestos y/o cuando sea aplicable a cada uno de sus estereoisómeros específicos y/o a sus tautómeros y/o a una de sus sales farmacéuticamente aceptables. Cada compuesto se representa y se considera en la forma del compuesto neutro sin indicar la estereoquímica del mismo si la hubiera. La columna del lado izquierdo indica el ejemplo del que se deriva el compuesto. Información específica sobre las propiedades estereoquímicas se puede obtener a partir de esta sección experimental, sección **Realizaciones ilustrativas**. En el caso de los compuestos finales que según dicha sección **de Realizaciones ilustrativas** son formas salinas, éstas se pueden convertir en el compuesto neutro (base o ácido libre) por métodos convencionales.

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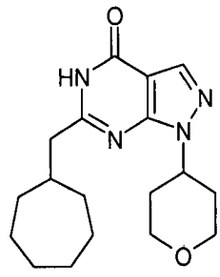
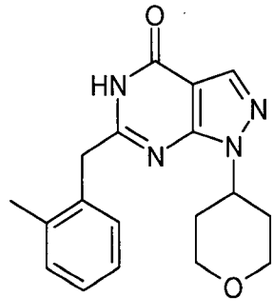
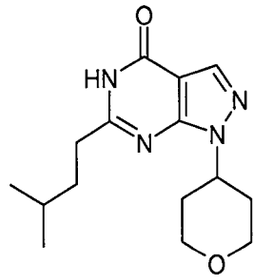
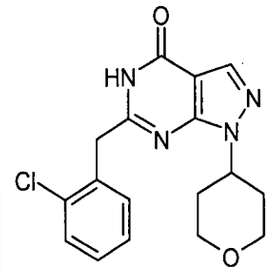
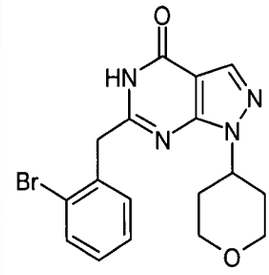
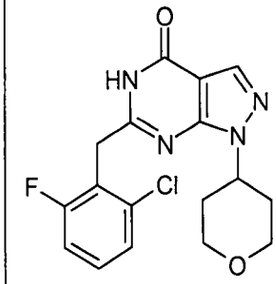
1	
2	
3	
4	
5	
6	

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R^{10} independientemente de cualquier otro **R^{10}** potencial se selecciona del grupo de

alquil C_{1-6}-, cicloalquil C_{3-7}-, arilo y heteroarilo,

y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos $-CH_2-$ del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})- preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2N$-CO-, estos dos R^{10} junto con dicho nitrógeno al que están unidos forman un grupo seleccionado entre piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,

y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cada uno de los otros **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cada uno de los otros **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales o solvatos farmacéuticamente aceptables.

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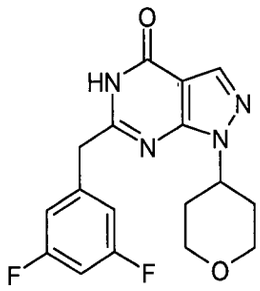
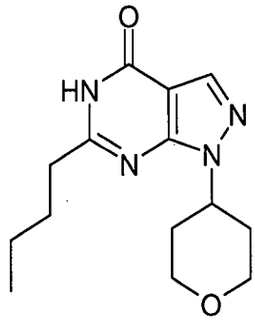
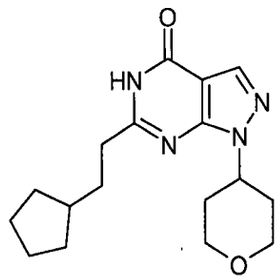
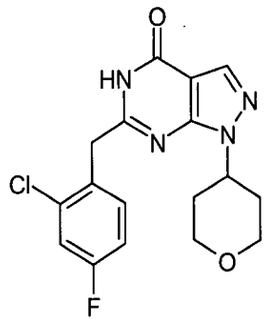
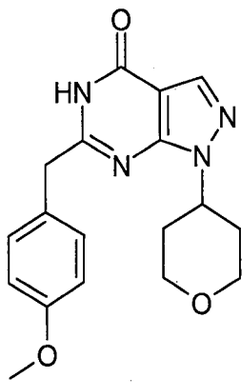
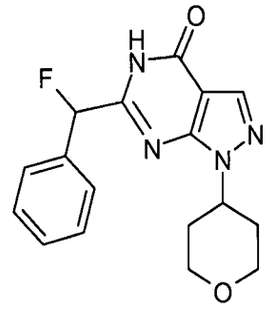
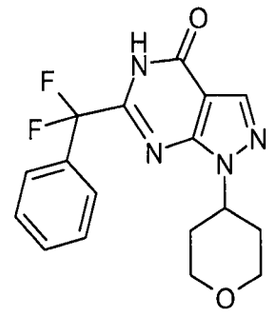
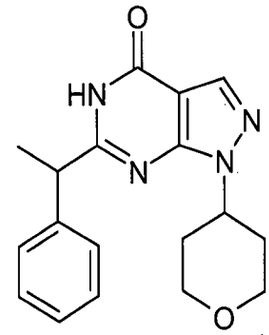
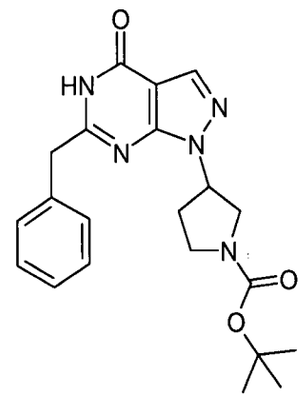
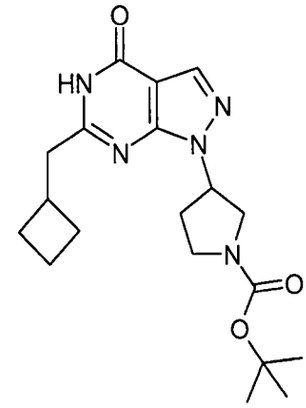
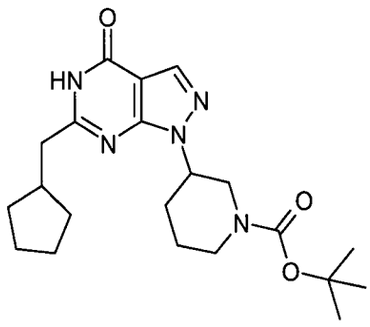
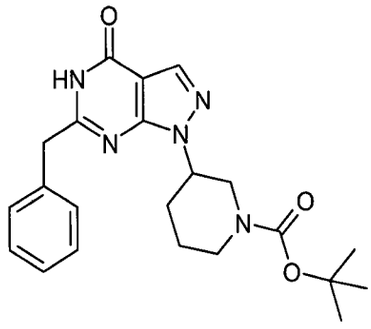
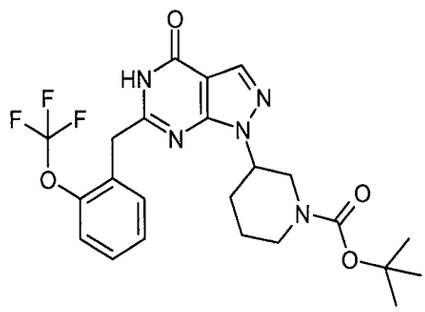
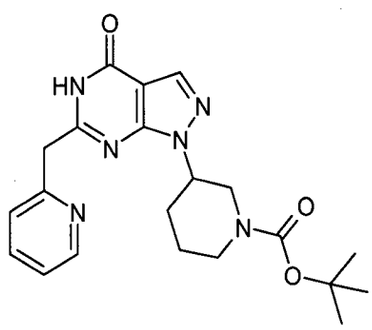
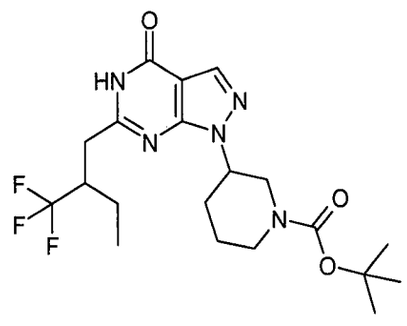
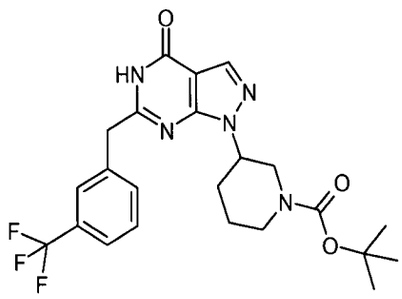
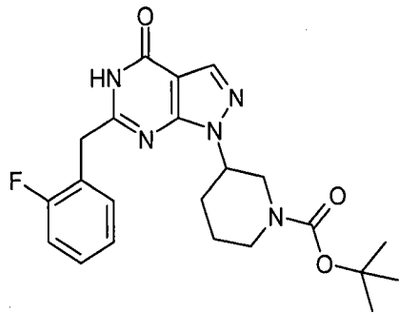
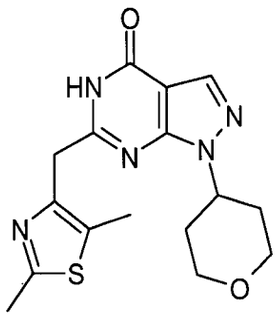
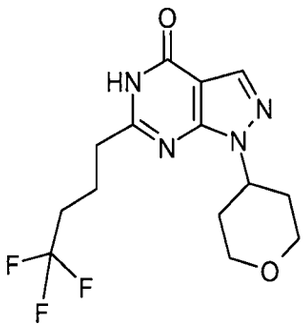
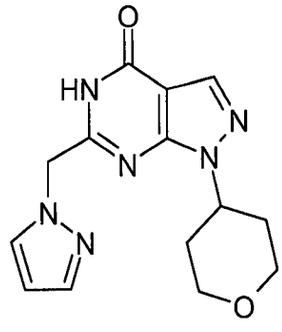
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	

17	
18	
19	
20	
21	

22	
23	
24	
25	
26	

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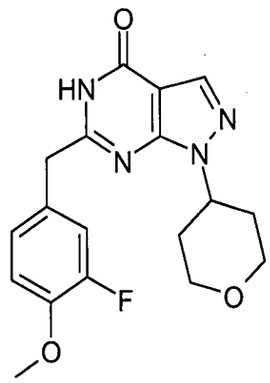
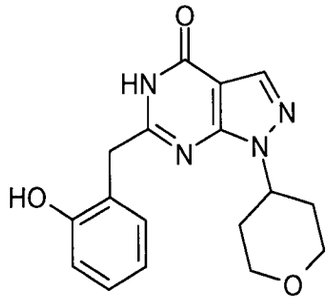
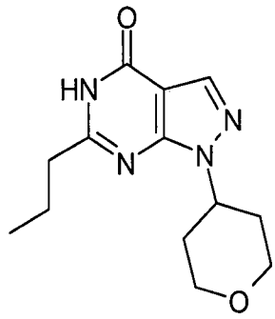
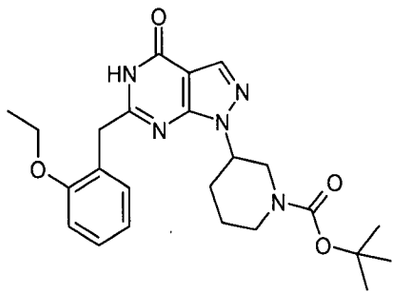
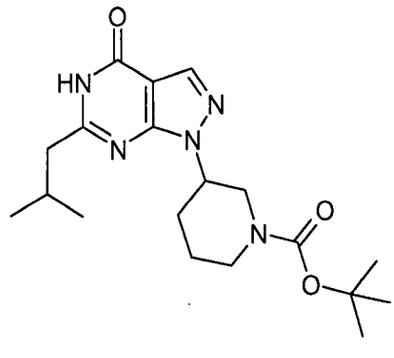
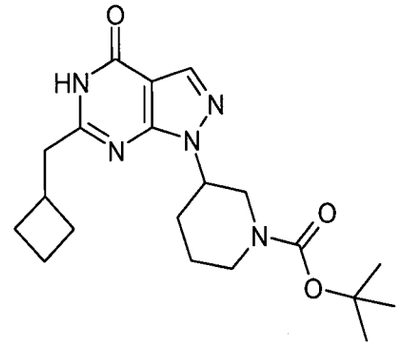
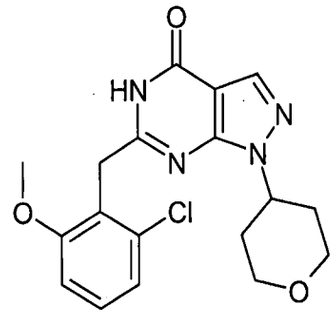
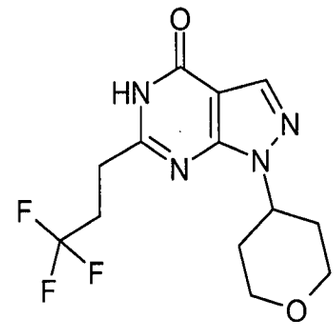
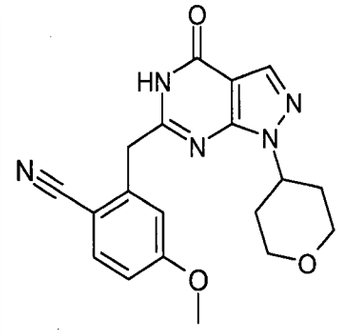
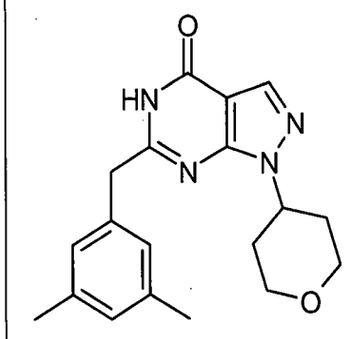
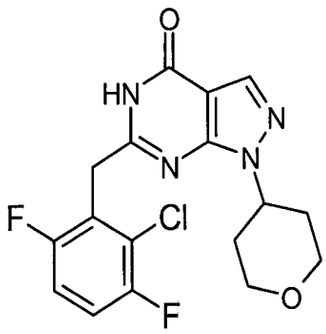
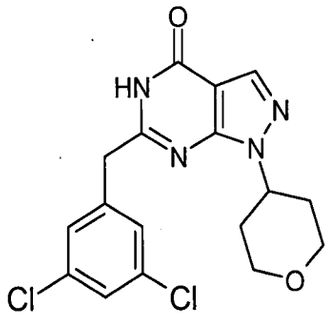
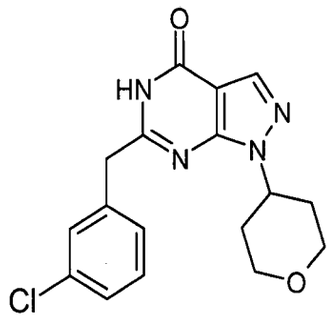
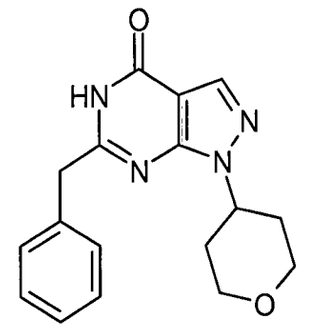
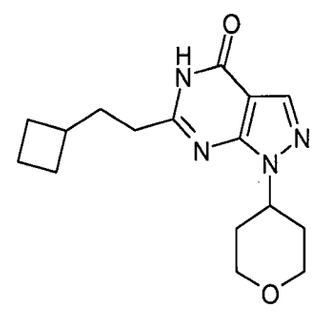
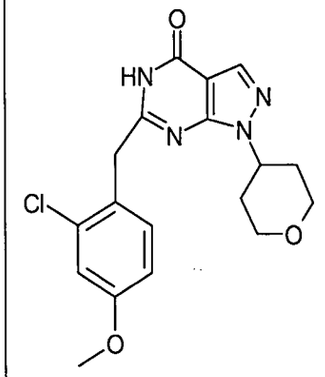
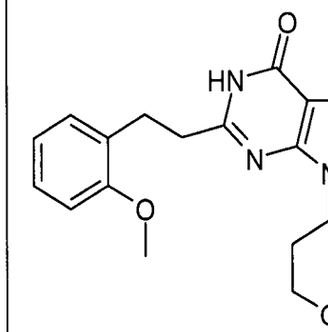
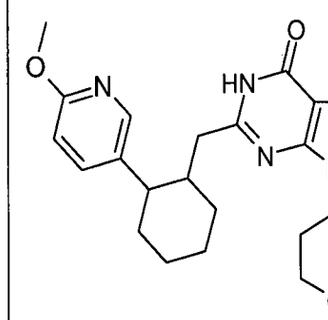
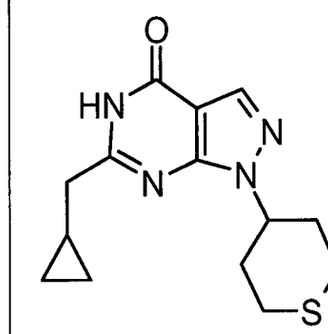
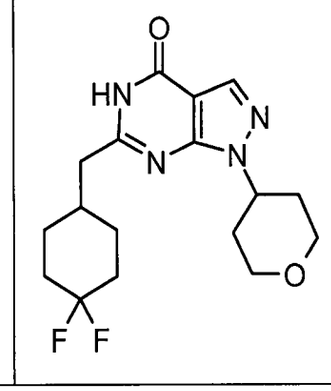
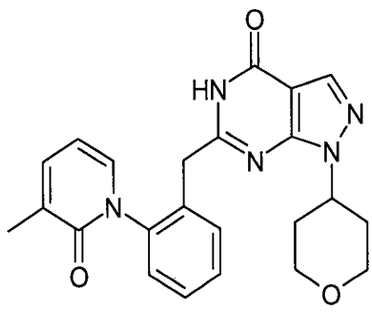
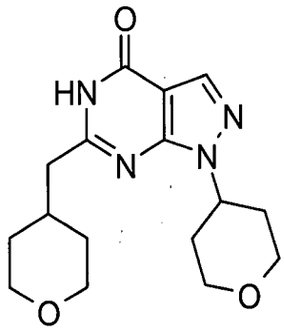
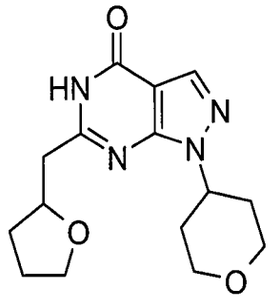
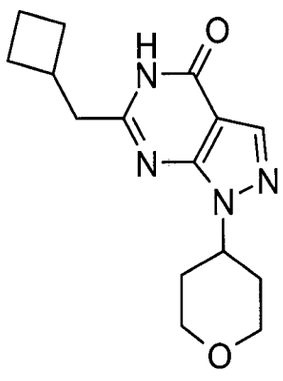
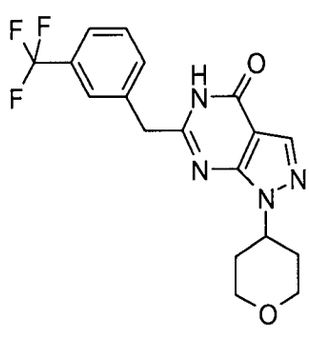
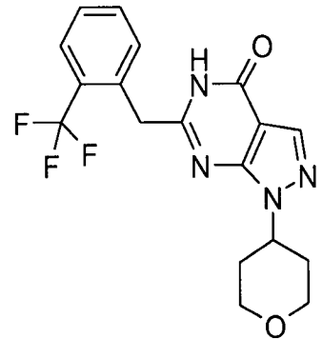
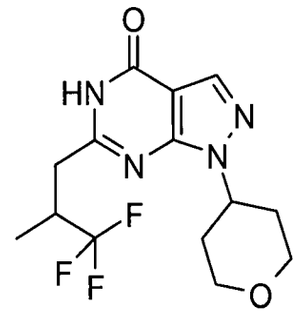
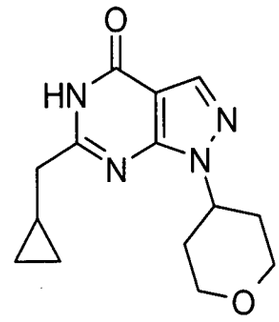
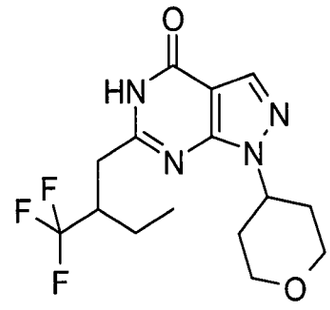
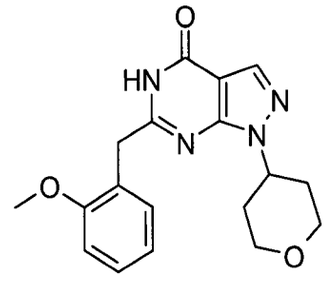
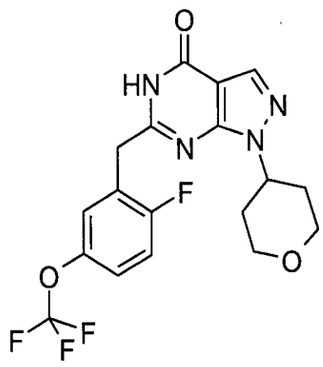
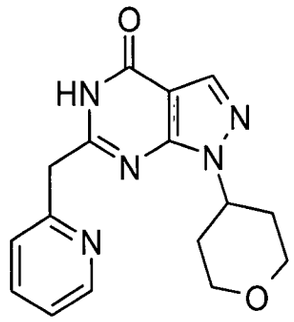
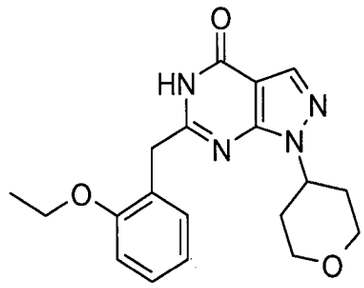
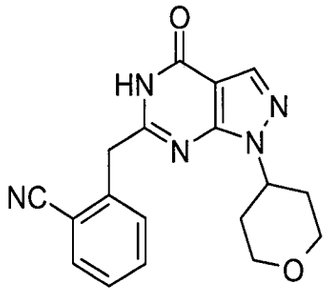
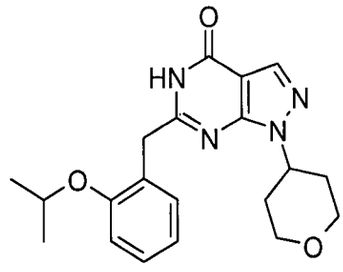
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	

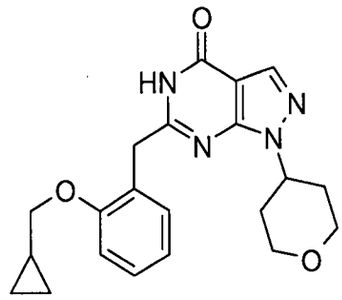
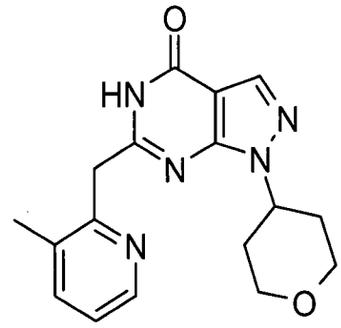
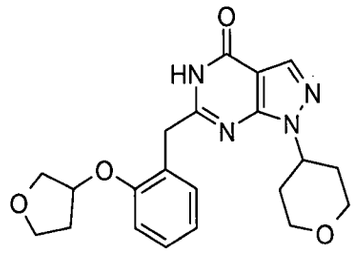
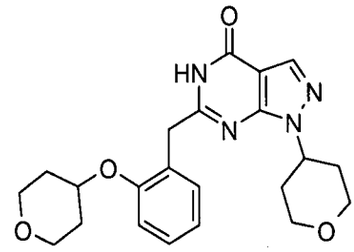
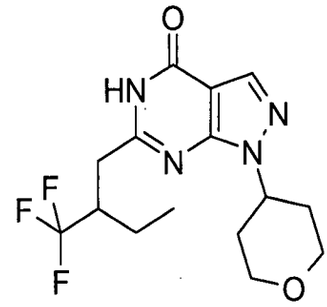
37	
38	
39	
40	
40-1	

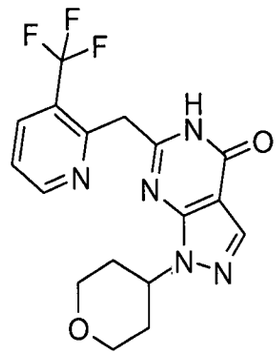
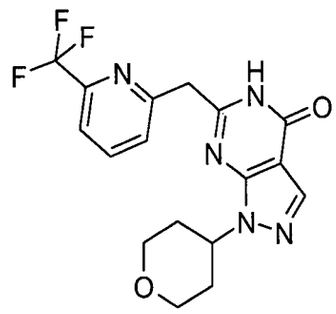
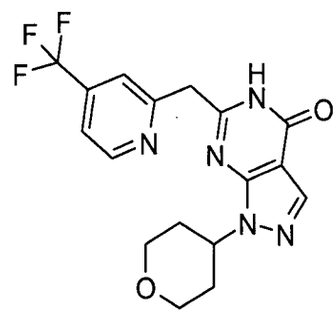
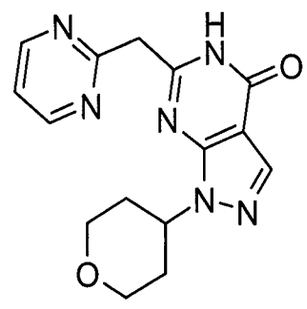
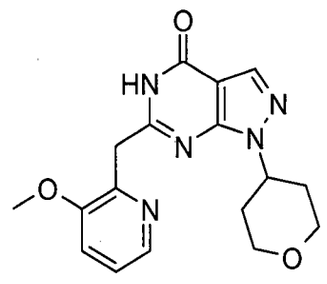
40-2	
40-3	
40-4	
40-5	
40-6	

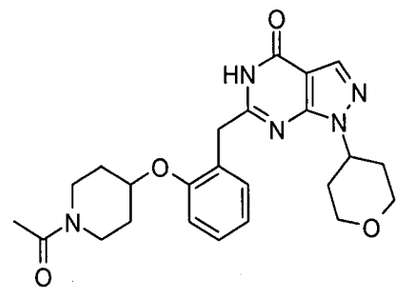
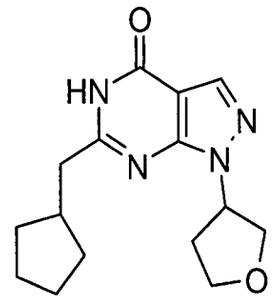
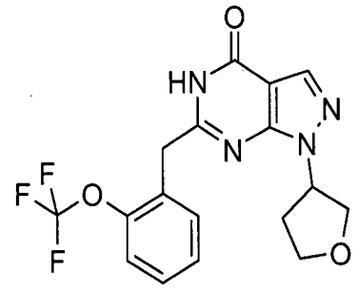
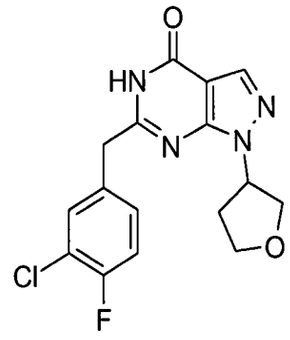
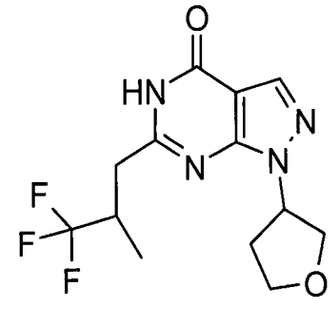
40-7	
41	
42	
43	
44	

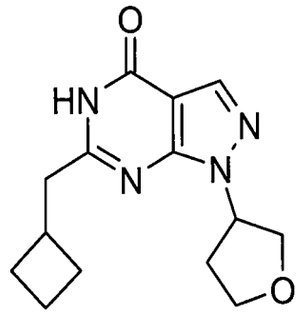
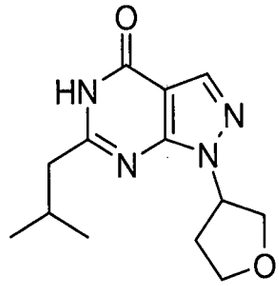
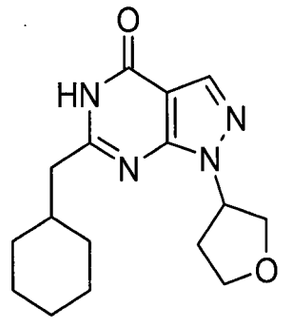
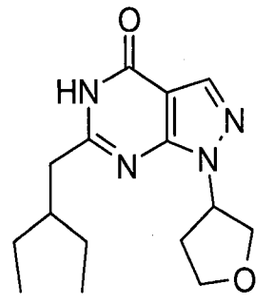
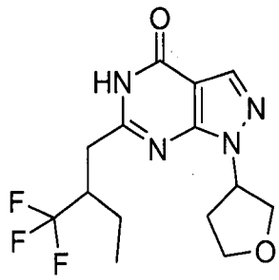
45	
46 & 131 & 132	
47	
48	
49	

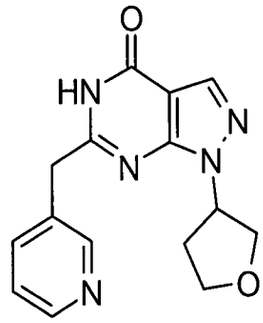
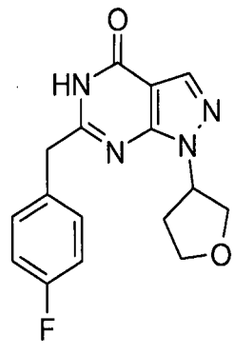
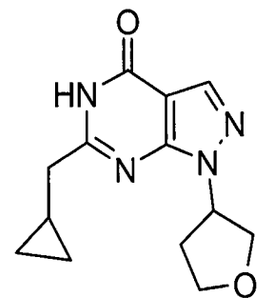
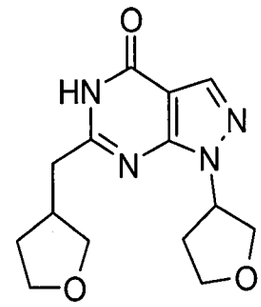
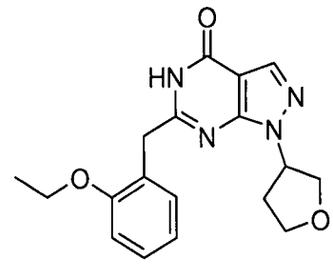
50	
51	
52	
53	
54	

55	
56	
57 & 58	
60	
61 & 62	

63	
64	
65	
66	
67	

68	
69	
70	
71	
72	

73	
74 & 132-3 & 132-4	
75	
76	
77	

78	
79	
80	
81	
82	

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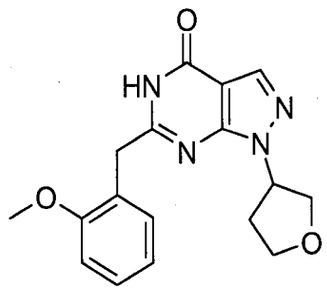
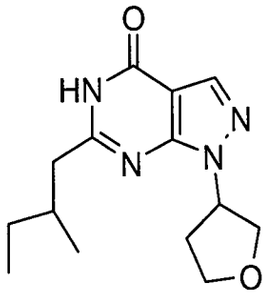
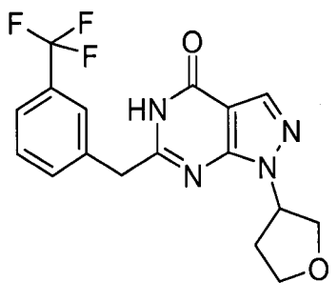
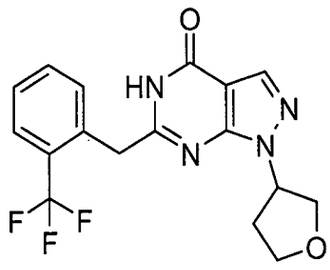
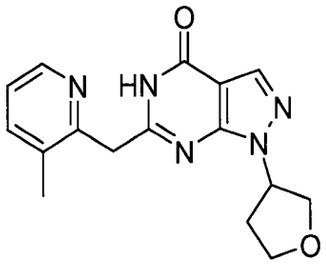
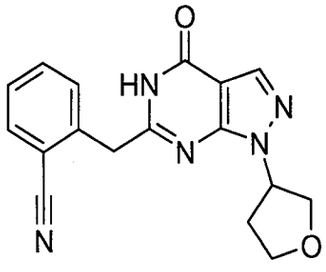
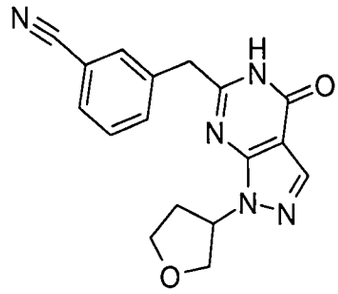
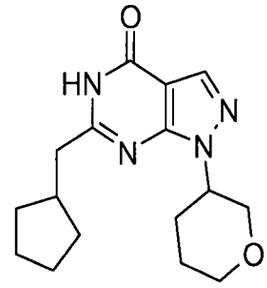
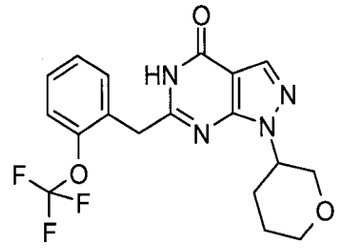
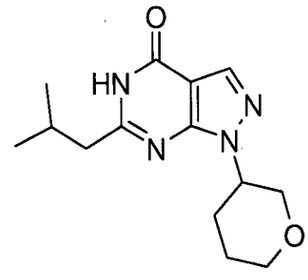
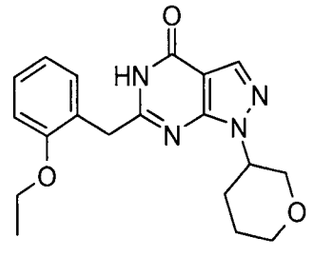
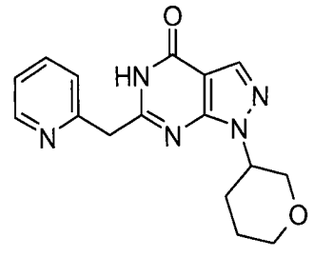
83	
84	
85	
86	
87	
88	
89	
90	
91	
92	
93	
94	

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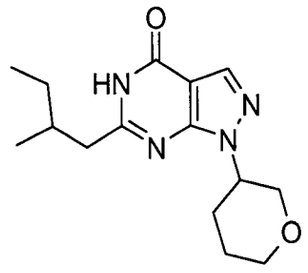
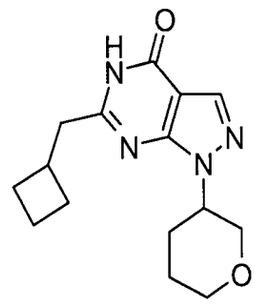
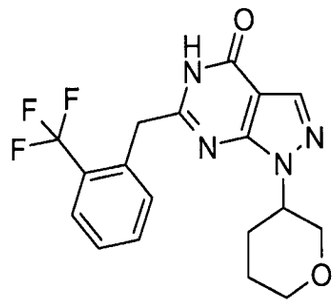
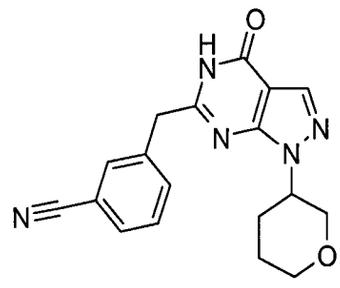
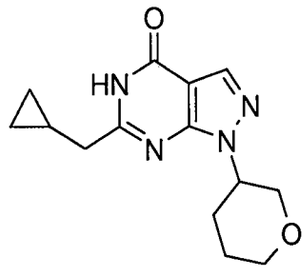
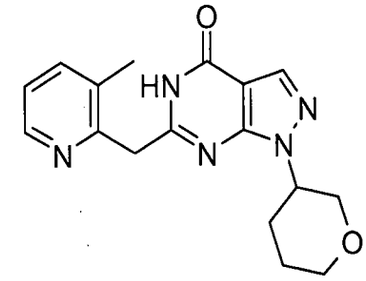
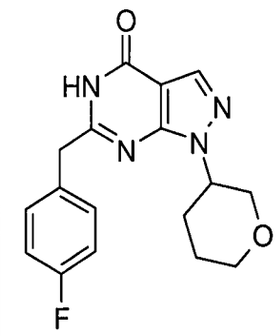
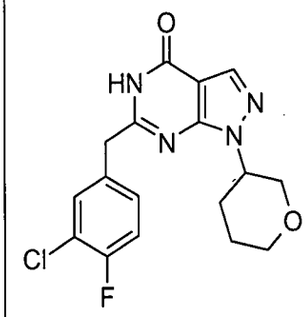
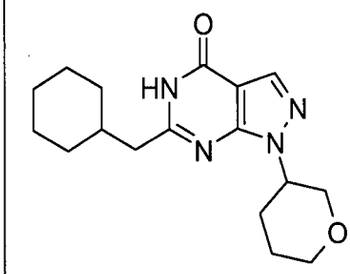
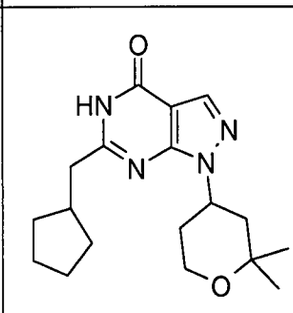
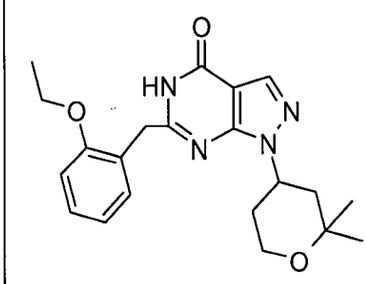
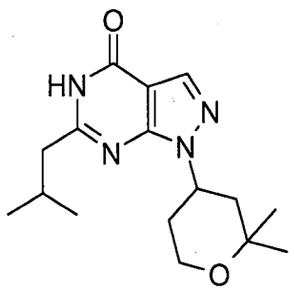
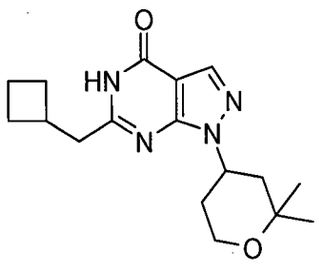
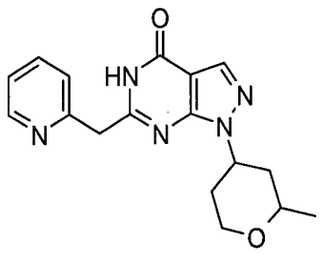
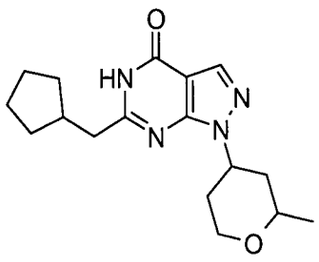
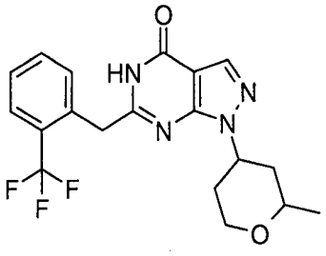
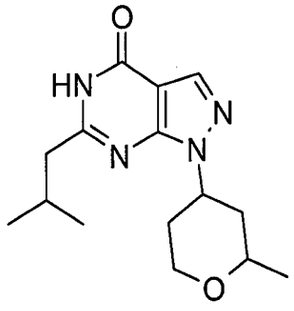
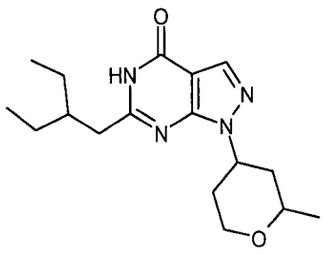
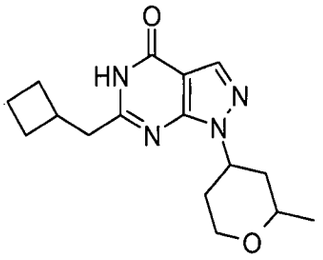
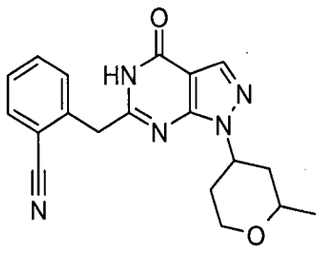
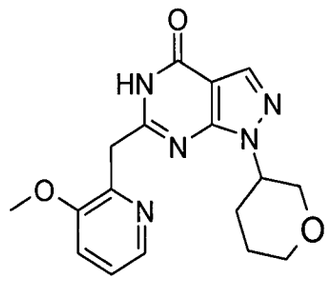
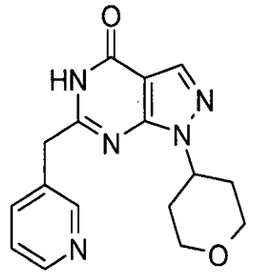
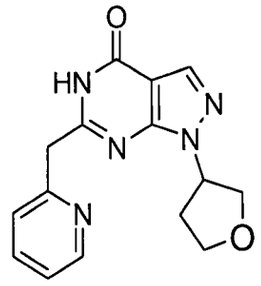
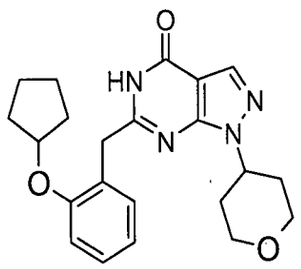
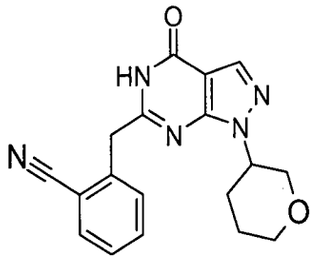
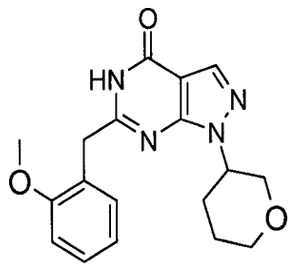
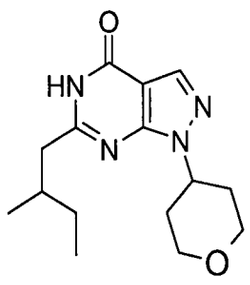
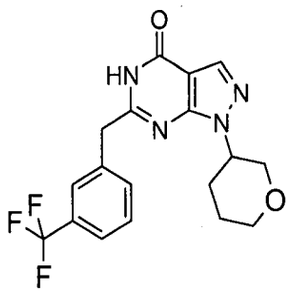
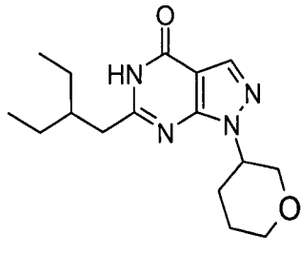
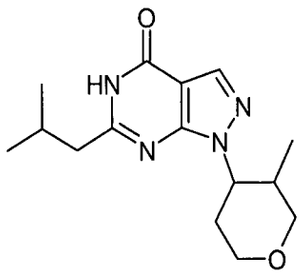
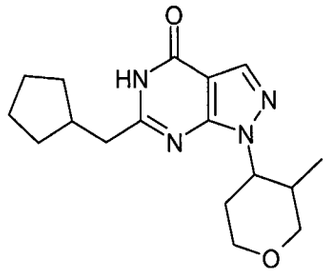
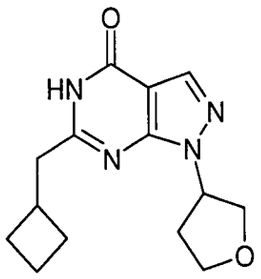
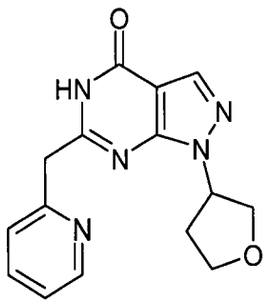
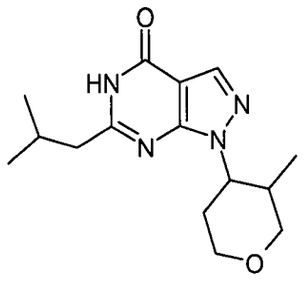
95	
96	
97	
98	
99	

100	
101	
102	
103	
104	
105	

106	
108	
111 & 118	
112 & 117	
113 & 116	
114 & 115	

119	
120	
121	
122	
123	
124	

125	
126	
127	
128	
129	
130	

132-1	
132-2 & 132-5	
132-6 & 132-9	
132-7	
132-8	

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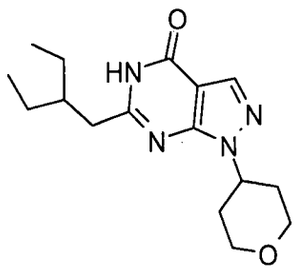
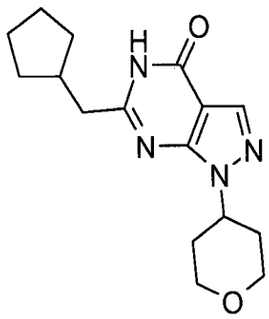
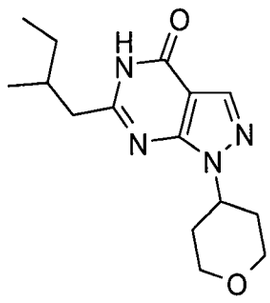
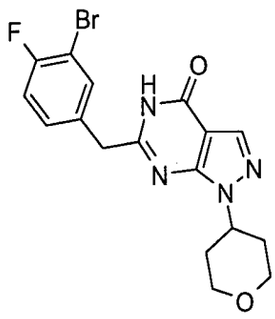
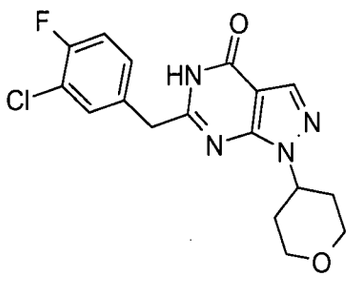
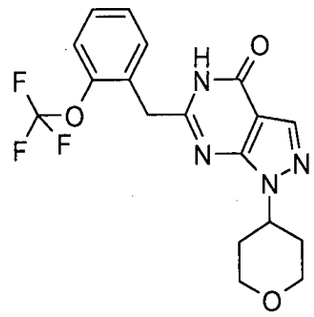
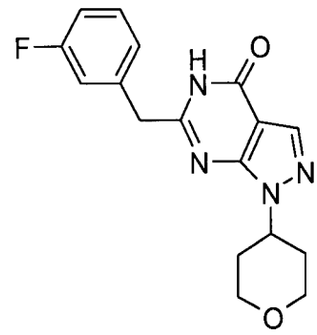
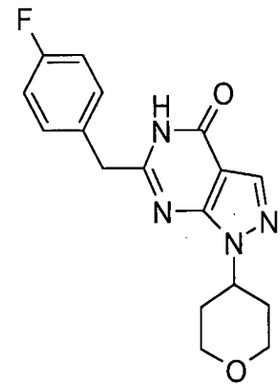
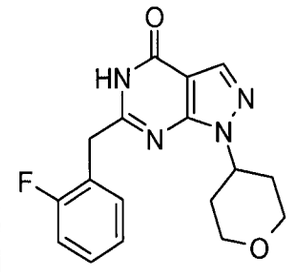
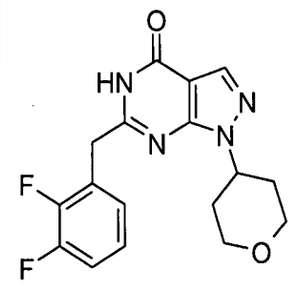
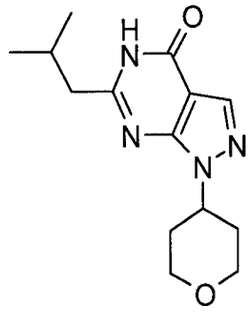
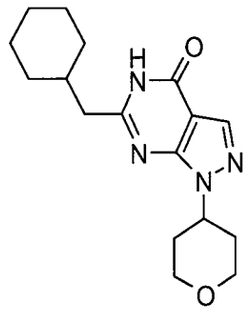
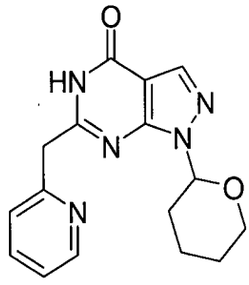
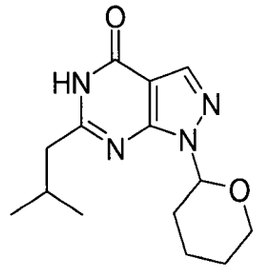
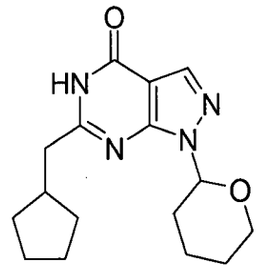
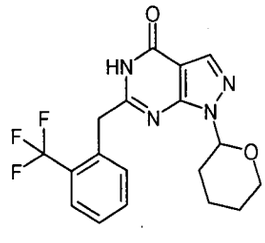
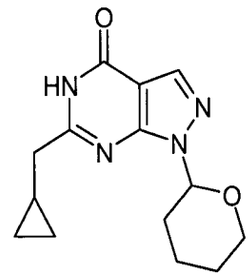
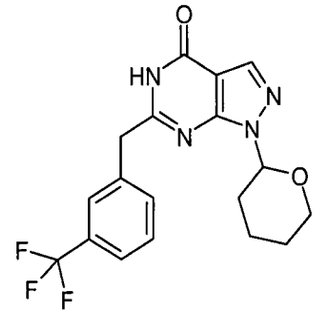
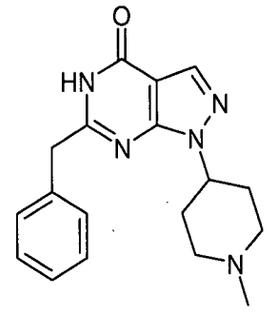
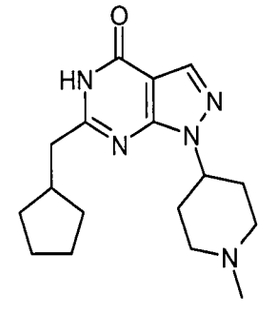
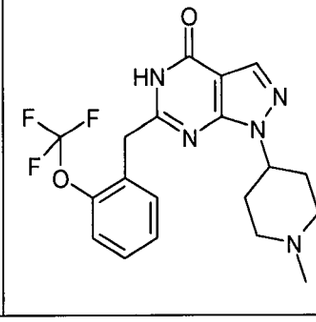
133	
134	
135	
136	
137	

138	
139	
140	
141	
142	

143	
144	
145	
146	
147	
147-1	

147-2	
147-3	
148	
149	
150	

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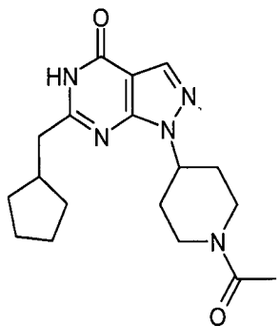
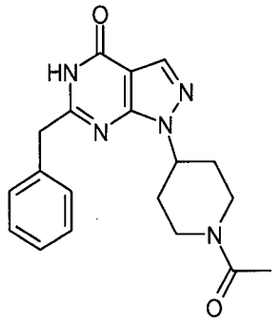
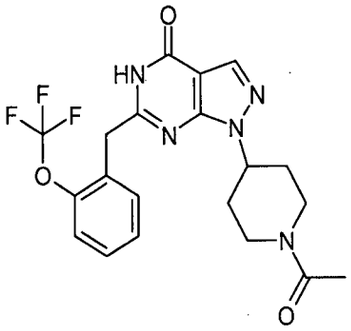
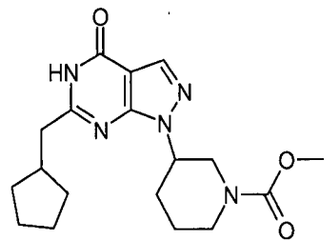
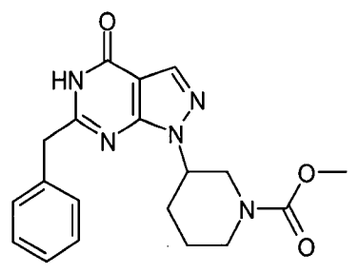
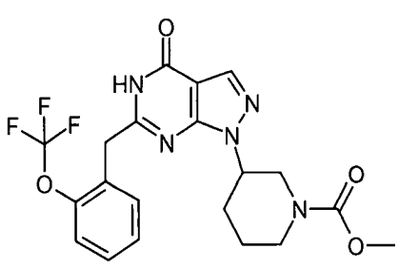
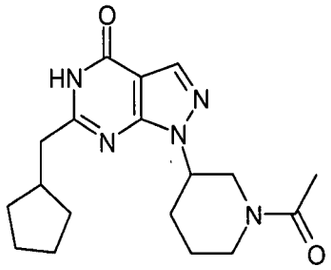
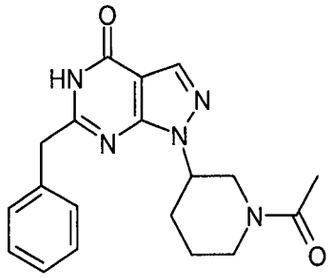
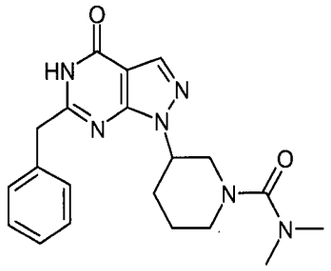
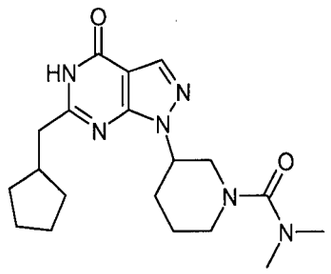
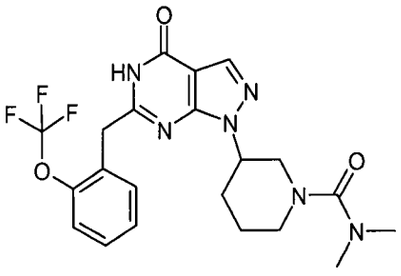
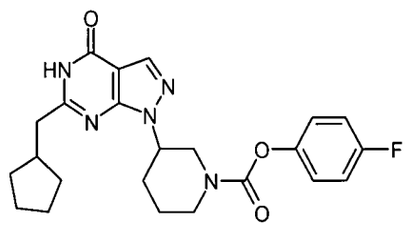
151	
152	
153	
154	
155	
156	

157	
158	
159	
160	
161	
162	

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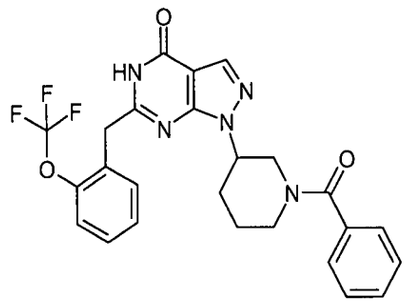
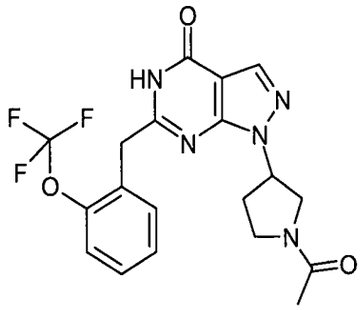
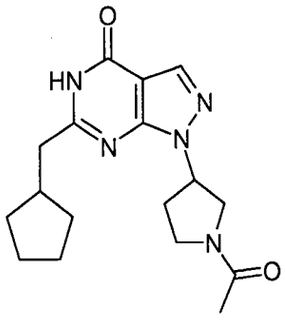
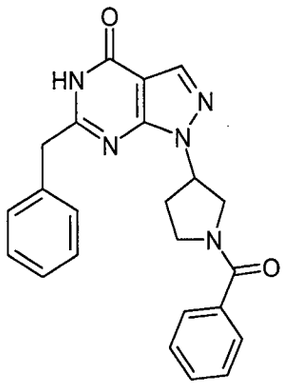
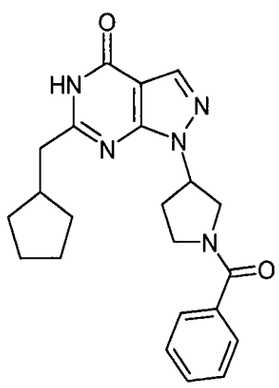
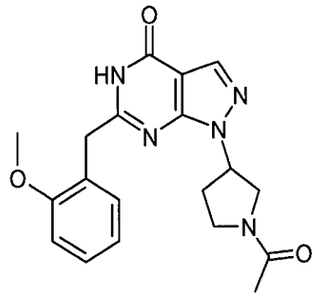
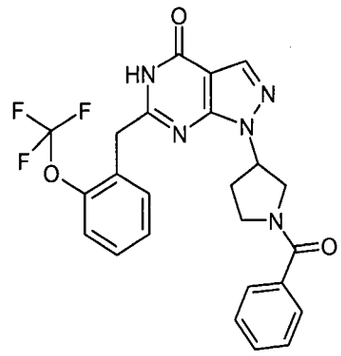
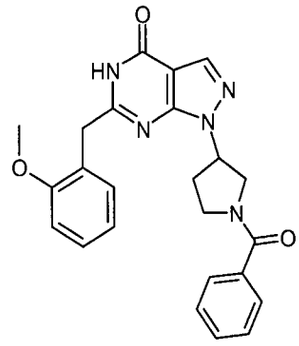
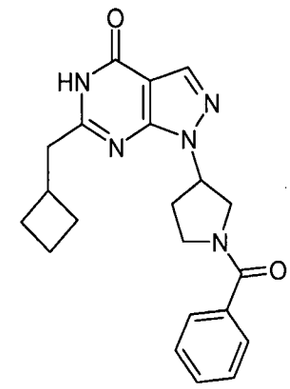
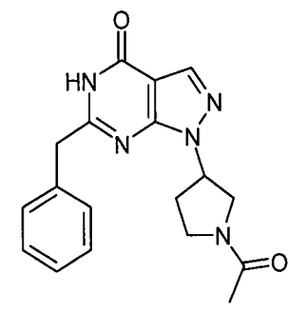
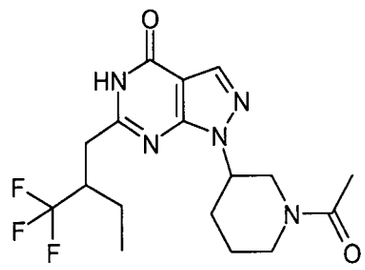
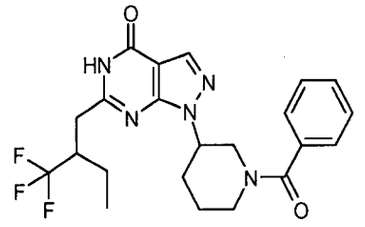
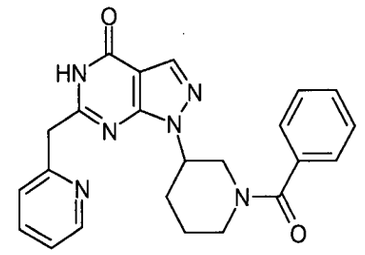
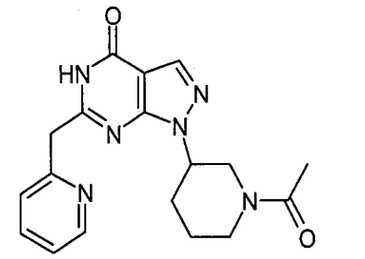
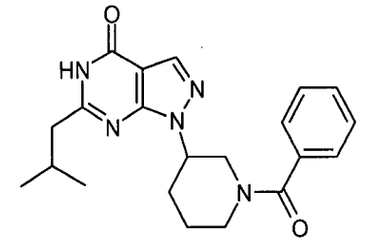
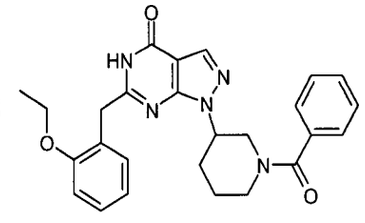
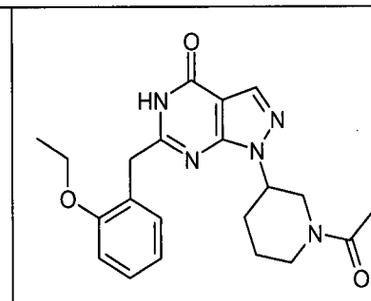
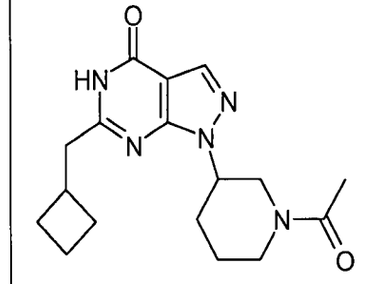
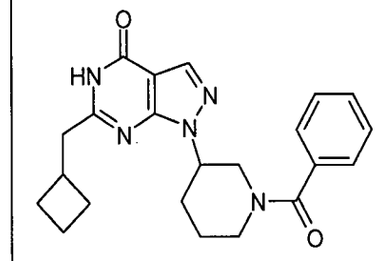
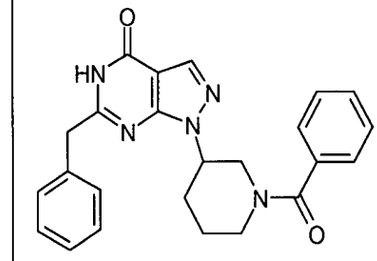
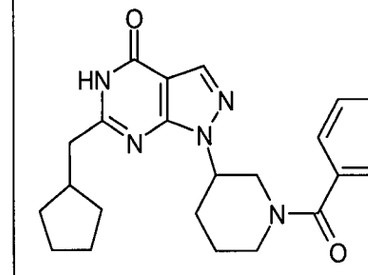
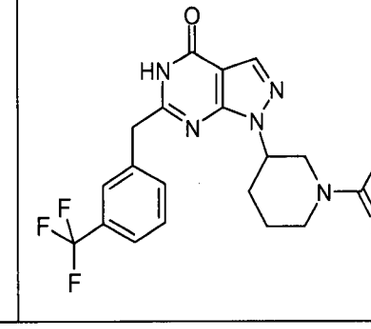
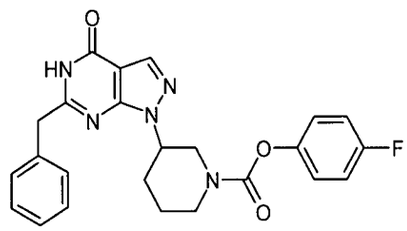
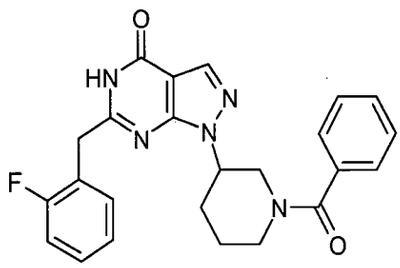
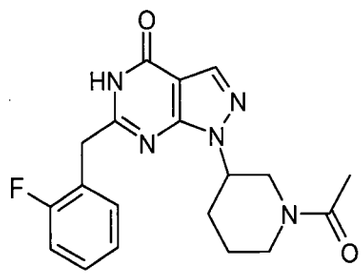
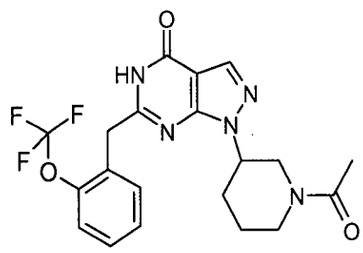
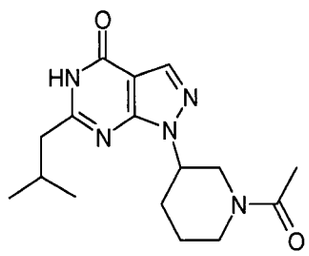
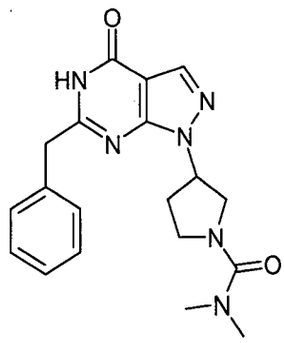
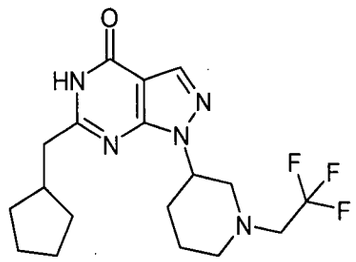
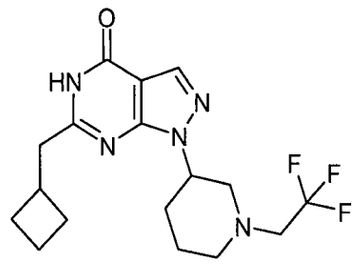
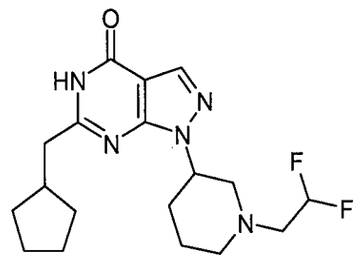
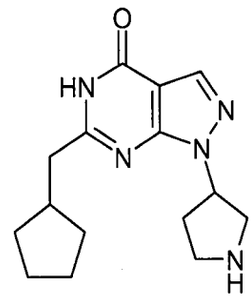
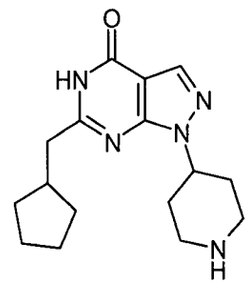
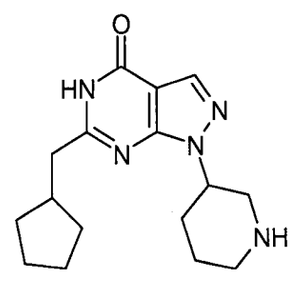
163	
164	
165	
166	
167	
168	
169	
170	
171	
172	

173	
174	
175	
176	
177	
178	

179	
180	
181	
182	
183	
184	

185	
186	
187	
188	
189	
190	

191,	
192	
193	
194	
195	
196	

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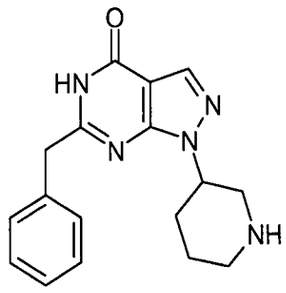
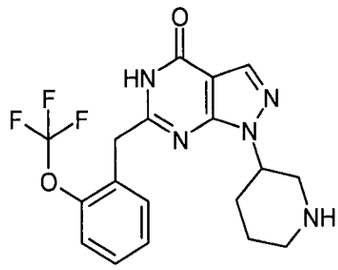
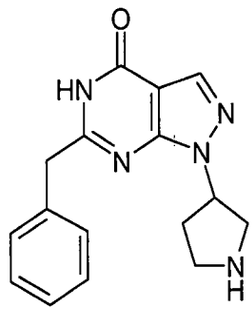
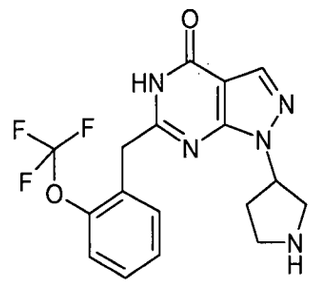
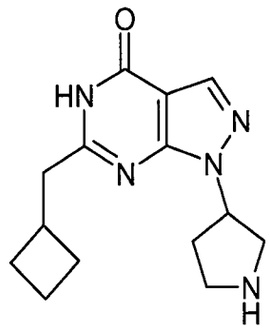
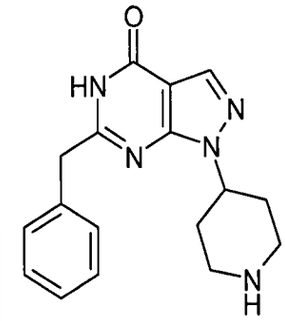
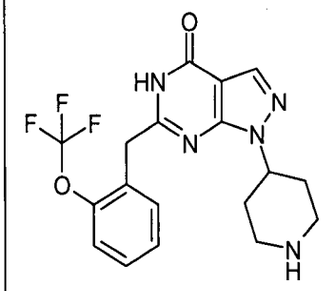
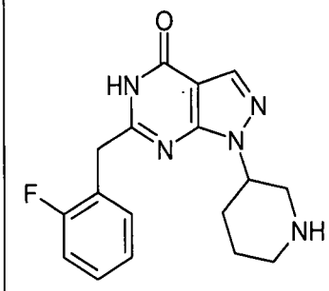
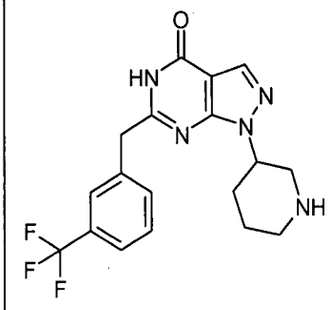
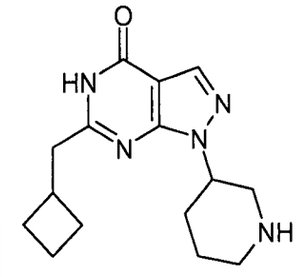
197	
198	
199	
200	
201	

202	
203	
204	
205	
206	

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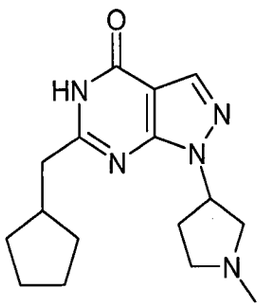
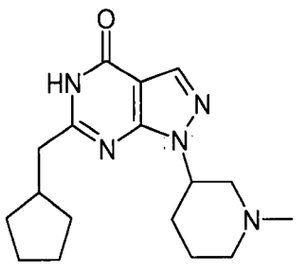
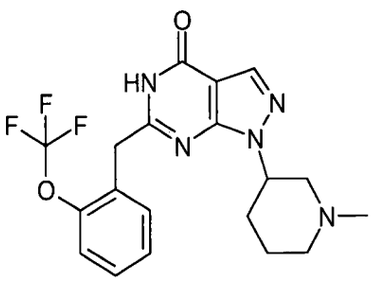
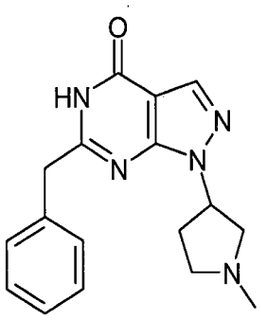
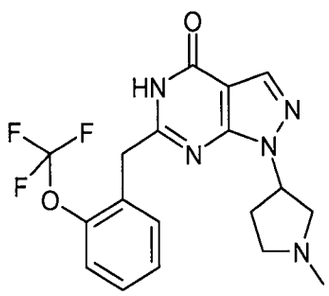
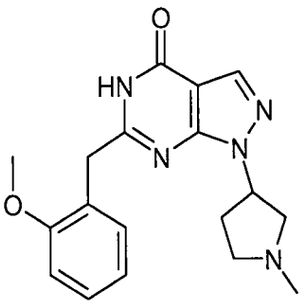
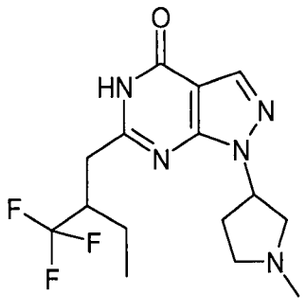
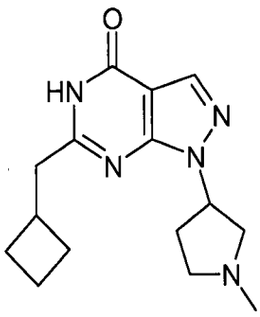
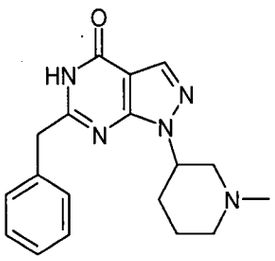
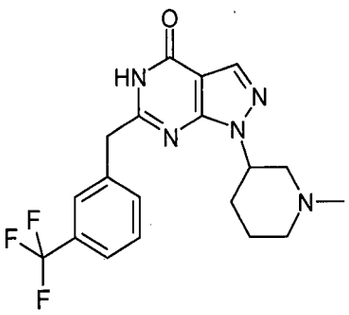
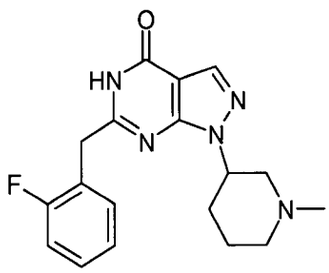
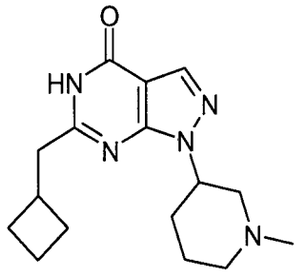
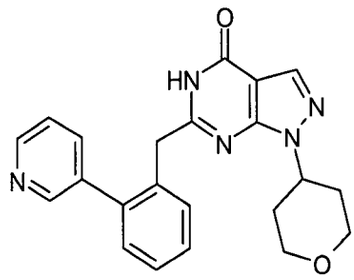
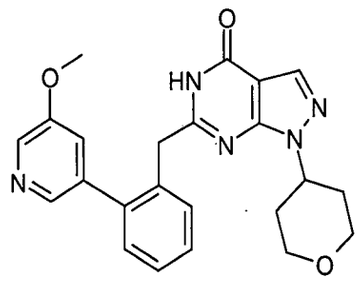
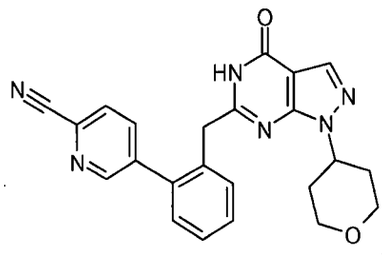
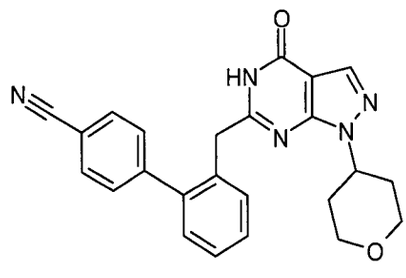
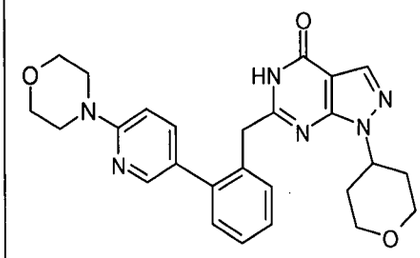
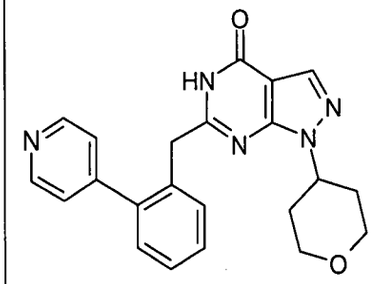
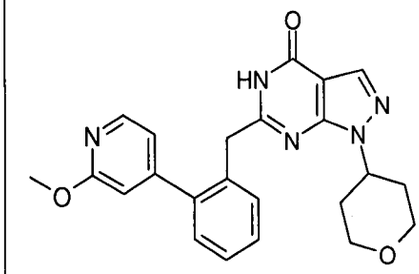
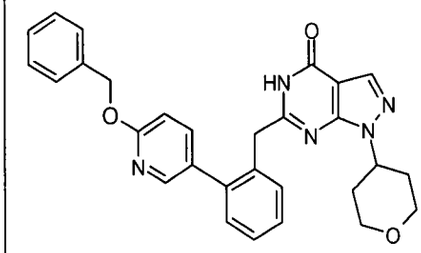
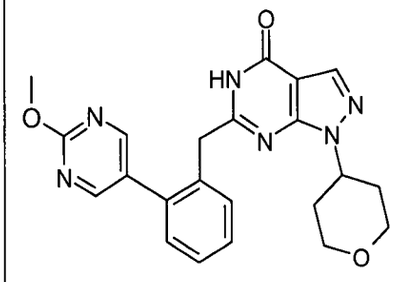
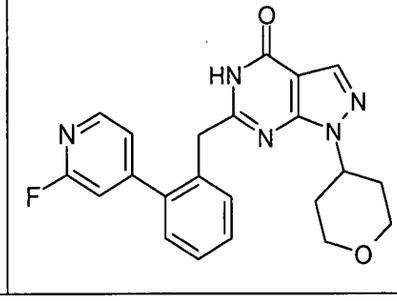
207	
208	
209	
210	
211	

212	
213	
214	
215	
216	

217	
218	
219	
220	
221	
222	

223	
224	
225	
226	
227	
228	

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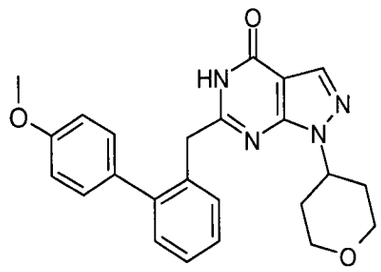
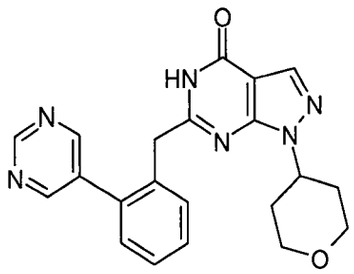
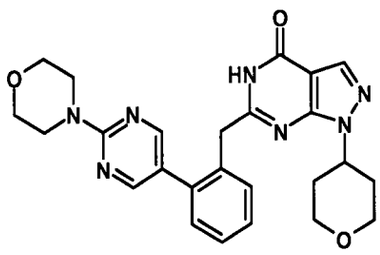
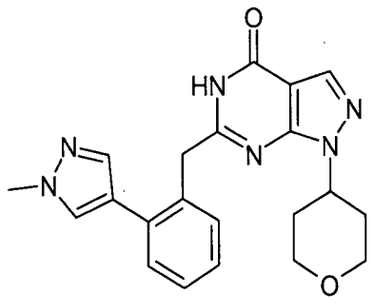
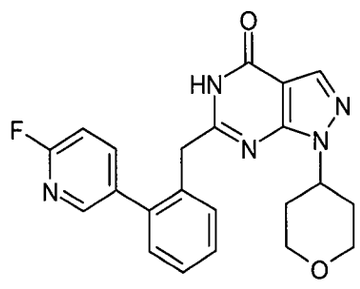
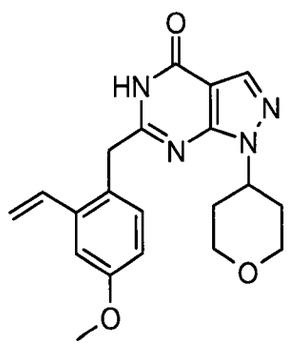
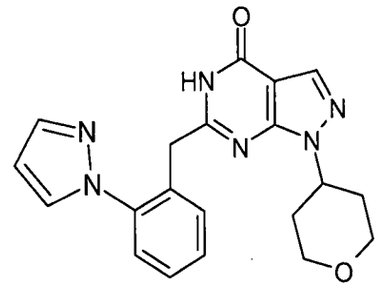
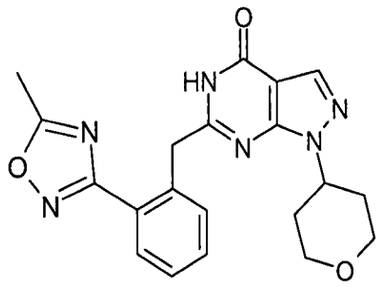
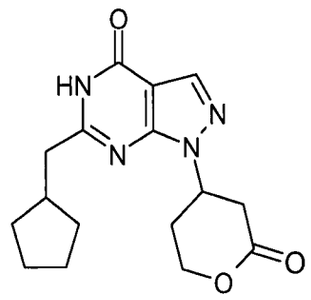
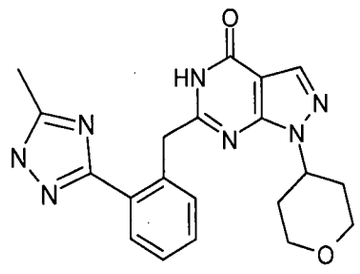
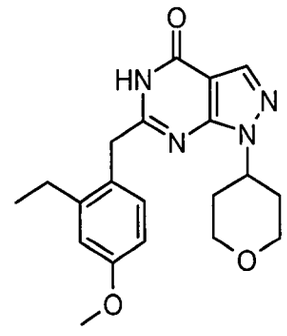
229	
230	
230-1	
230-2	
230-3	
230-4	

231	
232	
233	
234	
235	

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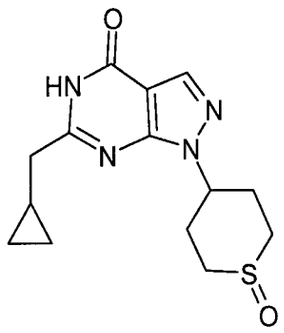
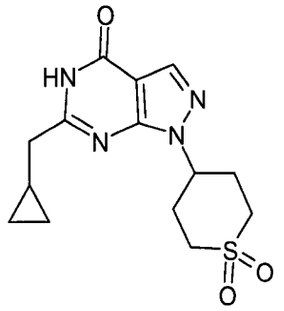
236	
237	

Estos 18 aspectos principales de la invención, sus subgrupos y algunos otros aspectos de la invención se listan como elementos de las siguientes matriz 0 y matriz I que hacen referencia a la numeración ($\underline{Hc}^{i}$ $R^{1.j}$ $R^{2.k}$ $R^{3.l}$ $R^{4/5.m}$ $R^{10.n}$), cuya lectura es como se ha definido antes, esto es, junto con la fórmula general I y las restantes características como x, y, como se indica directamente debajo de dicha matriz 0 o matriz I.

La matriz 0 y la matriz I muestran en la columna del lado derecho las realizaciones ($\underline{Hc}^{i}$ $R^{1.j}$ $R^{2.k}$ $R^{3.l}$ $R^{4/5.m}$ $R^{10.n}$) de la invención según la fórmula general I que se consideran preferidas, independientes y separables una de otra, esto es, aspectos individuales de la invención. La columna del lado izquierdo proporciona un número de referencia para tales realizaciones. Las realizaciones o elementos se listan en orden desde los menos preferidos a los más preferidos, la preferencia de las realizaciones asciende con el número de referencia. Esto significa que la realización, que se presenta por el elemento de la matriz en la última fila, la última entrada de la matriz 0 o de la matriz I es la realización más preferida, mientras que las realizaciones de la matriz I son preferidas sobre las realizaciones de la matriz 0.

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Los aspectos 1 a 18 son los principales aspectos de la invención.

Matriz 0

La primera realización de esta matriz 0 representa el primer aspecto general de la invención. Las siguientes realizaciones son subconjuntos de la misma.

No.	Realización
M0-001	$\underline{Hc}^{1}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-002	$\underline{Hc}^{2}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-003	$\underline{Hc}^{2}R^{1.0.2}R^{2.3}R^{3.3}R^{4/5.2}R^{10.0.2}$
M0-004	$\underline{Hc}^{3}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.0.3}$
M0-005	$\underline{Hc}^{3}R^{1.0.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.0.3}$
M0-006	$\underline{Hc}^{7.0}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-007	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.1}R^{3.1}R^{4/5.2}R^{10.0.2}$
M0-008	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-009	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-010	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.4}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-011	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-012	$\underline{Hc}^{7.0}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-013	$\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-014	$\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-015	$\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-016	$\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$
M0-017	$\underline{Hc}^{7.0}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-018	$\underline{Hc}^{7.1}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-019	$\underline{Hc}^{7.1}R^{1.0.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-020	$\underline{Hc}^{7.1}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-021	$\underline{Hc}^{7.1}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-022	$\underline{Hc}^{7.1}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-023	$\underline{Hc}^{7.1}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-024	$\underline{Hc}^{7.1}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-025	$\underline{Hc}^{7.1}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$
M0-026	$\underline{Hc}^{7.1}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-027	$\underline{Hc}^{7.1}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$
M0-028	$\underline{Hc}^{8}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-029	$\underline{Hc}^{8}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-030	$\underline{Hc}^{8}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-031	$\underline{Hc}^{8}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-032	$\underline{Hc}^{8}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-033	$\underline{Hc}^{8}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-034	$\underline{Hc}^{8}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-035	$\underline{Hc}^{8}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$

M0-036	$\underline{Hc}^{8}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-037	$\underline{Hc}^{8}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$
M0-038	$\underline{Hc}^{9}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-039	$\underline{Hc}^{9}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-040	$\underline{Hc}^{9}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-041	$\underline{Hc}^{9}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-042	$\underline{Hc}^{9}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-043	$\underline{Hc}^{9}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-044	$\underline{Hc}^{9}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-045	$\underline{Hc}^{9}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$
M0-046	$\underline{Hc}^{9}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-047	$\underline{Hc}^{9}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$
M0-048	$\underline{Hc}^{9}R^{1.4}R^{2.4}R^{3.2}R^{4/5.2}R^{10.4}$
M0-049	$\underline{Hc}^{9}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
M0-050	$\underline{Hc}^{9}R^{1.4}R^{2.4}R^{3.3}R^{4/5.2}R^{10.4}$
M0-051	$\underline{Hc}^{9}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$

M0-052	$\underline{Hc}^{10}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$
M0-053	$\underline{Hc}^{10}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$
M0-054	$\underline{Hc}^{10}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-055	$\underline{Hc}^{10}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-056	$\underline{Hc}^{10}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$
M0-057	$\underline{Hc}^{10}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$
M0-058	$\underline{Hc}^{10}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$
M0-059	$\underline{Hc}^{10}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$
M0-060	$\underline{Hc}^{10}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-061	$\underline{Hc}^{10}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$
M0-062	$\underline{Hc}^{10}R^{1.4}R^{2.4}R^{3.2}R^{4/5.2}$
M0-063	$\underline{Hc}^{10}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}$
M0-064	$\underline{Hc}^{10}R^{1.4}R^{2.4}R^{3.3}R^{4/5.2}$
M0-065	$\underline{Hc}^{10}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$
M0-066	$\underline{Hc}^{10}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$

donde para cada realización de la matriz 0:

x independientemente de cada uno de los otros = 0, 1, 2, 3 o 4, preferiblemente x = 0, 1 o 2; preferiblemente es 0 o 1, más preferiblemente x= 0:

y independientemente de cada uno de los otros y = 0, o 1; más preferiblemente y= 0, donde las definiciones específicas con las realizaciones de la matriz prevalecen;

y sus sales y/o solvatos farmacéuticamente aceptables.

y con la condición de que - para cada realización de la matriz 0 para la que esta condición es aplicable - tal como para las realizaciones que comprenden ***Hc*** como se define por $\underline{Hc}^1$ o $\underline{Hc}^3$ -

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador $-CH_2-$.

Debe ser evidente, que si x y/o y = 0 entonces ***Hc*** está insustituido, esto es, las correspondientes valencias de los átomos miembros del anillo están saturadas por hidrógeno.

En el caso de que R^{10} no esté suficientemente definido en la matriz 0 será $R^{10.0.4}$ o $R^{10.0.5}$, preferiblemente $R^{10.0.5}$.

matriz I:

No.	Realización
MI-001	$\underline{Hc}^1R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-002	$\underline{Hc}^2R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-003	$\underline{Hc}^2R^{1.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.2}$
MI-004	$\underline{Hc}^2R^{1.2}R^{2.3}R^{3.3}R^{4/5.2}R^{10.2}$
MI-005	$\underline{Hc}^3R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-006	$\underline{Hc}^3R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-007	$\underline{Hc}^3R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-008	$\underline{Hc}^3R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-009	$\underline{Hc}^3R^{1.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-010	$\underline{Hc}^3R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-011	$\underline{Hc}^3R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-012	$\underline{Hc}^3R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$
MI-013	$\underline{Hc}^3R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-014	$\underline{Hc}^3R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-015	$\underline{Hc}^3R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-016	$\underline{Hc}^3R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-017	$\underline{Hc}^3R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-018	$\underline{Hc}^3R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$
MI-019	$\underline{Hc}^3R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$
MI-020	$\underline{Hc}^3R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-021	$\underline{Hc}^3R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$

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MI-022	$\underline{Hc}^{3}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-023	$\underline{Hc}^{3}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-024	$\underline{Hc}^{3}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-025	$\underline{Hc}^{3}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$
MI-026	$\underline{Hc}^{3}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$
MI-027	$\underline{Hc}^{4}R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-028	$\underline{Hc}^{4}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-029	$\underline{Hc}^{4}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-030	$\underline{Hc}^{4}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-031	$\underline{Hc}^{4}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-032	$\underline{Hc}^{4}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-033	$\underline{Hc}^{4}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-034	$\underline{Hc}^{4}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-035	$\underline{Hc}^{4}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-036	$\underline{Hc}^{4}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-037	$\underline{Hc}^{4}R^{1.2}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-038	$\underline{Hc}^{4}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-039	$\underline{Hc}^{4}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$
MI-040	$\underline{Hc}^{4}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-041	$\underline{Hc}^{4}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-042	$\underline{Hc}^{4}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-043	$\underline{Hc}^{4}R^{1.3}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-044	$\underline{Hc}^{4}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-045	$\underline{Hc}^{4}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-046	$\underline{Hc}^{4}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$
MI-047	$\underline{Hc}^{4}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$
MI-048	$\underline{Hc}^{4}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-049	$\underline{Hc}^{4}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-050	$\underline{Hc}^{4}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-051	$\underline{Hc}^{4}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-052	$\underline{Hc}^{4}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-053	$\underline{Hc}^{4}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$
MI-054	$\underline{Hc}^{4}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$
MI-055	$\underline{Hc}^{7.1}R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-056	$\underline{Hc}^{7.1}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-057	$\underline{Hc}^{7.1}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-058	$\underline{Hc}^{7.1}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-059	$\underline{Hc}^{7.1}R^{1.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-060	$\underline{Hc}^{7.1}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-061	$\underline{Hc}^{7.1}R^{1.2}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-062	$\underline{Hc}^{7.1}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-063	$\underline{Hc}^{7.1}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$
MI-064	$\underline{Hc}^{7.1}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-065	$\underline{Hc}^{7.1}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-066	$\underline{Hc}^{7.1}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-067	$\underline{Hc}^{7.1}R^{1.3}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$

MI-068	$\underline{Hc}^{7.1}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-069	$\underline{Hc}^{7.1}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-070	$\underline{Hc}^{7.1}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$
MI-071	$\underline{Hc}^{7.1}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$
MI-072	$\underline{Hc}^{7.1}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-073	$\underline{Hc}^{7.1}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-074	$\underline{Hc}^{7.1}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-075	$\underline{Hc}^{7.1}R^{1.4}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-076	$\underline{Hc}^{7.1}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-077	$\underline{Hc}^{7.1}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-078	$\underline{Hc}^{7.1}R^{1.4}R^{2.5}R^{3.2}R^{4/5.34}$
MI-079	$\underline{Hc}^{7.1}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$
MI-080	$\underline{Hc}^{8}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-081	$\underline{Hc}^{8}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-082	$\underline{Hc}^{8}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-083	$\underline{Hc}^{8}R^{1.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-084	$\underline{Hc}^{8}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-085	$\underline{Hc}^{8}R^{1.2}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$

MI-086	$\underline{Hc}^{8}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$
MI-087	$\underline{Hc}^{8}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$
MI-088	$\underline{Hc}^{8}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-089	$\underline{Hc}^{8}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-090	$\underline{Hc}^{8}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-091	$\underline{Hc}^{8}R^{1.3}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-092	$\underline{Hc}^{8}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-093	$\underline{Hc}^{8}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-094	$\underline{Hc}^{8}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$
MI-095	$\underline{Hc}^{8}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$
MI-096	$\underline{Hc}^{8}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$
MI-097	$\underline{Hc}^{8}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$
MI-098	$\underline{Hc}^{8}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$
MI-099	$\underline{Hc}^{8}R^{1.4}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$
MI-100	$\underline{Hc}^{8}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$
MI-101	$\underline{Hc}^{8}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$
MI-102	$\underline{Hc}^{8}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$
MI-103	$\underline{Hc}^{8}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$

donde para cada realización de la matriz I:

x independientemente de cada uno de los otros = 0, 1, 2, 3 o 4, preferiblemente x = 0, 1 o 2;

y independientemente de cada uno de los otros y = 0 o 1;

y sus sales y/o solvatos farmacéuticamente aceptables.

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y con la condición de que - para cada realización de la matriz 0 para la que esta condición es aplicable - tal como para las realizaciones que comprenden ***Hc*** como se define por $\underline{Hc}^1$ o $\underline{Hc}^3$ -

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador $-CH_2-$.

Debe ser evidente, que si x y/o y = 0 entonces ***Hc*** está insustituido, esto es, las correspondientes valencias de los átomos miembros del anillo están saturadas por hidrógeno.

En el caso de que R^{10} no esté suficientemente definido en la matriz I será $R^{10.4}$.

Realizaciones adicionales según la invención y subconjunto de los aspectos 1 a 17 y las realizaciones de la matriz 0 o de la matriz I

A continuación se presentan realizaciones adicionales de la invención. Cada una es independiente y separable, esto es, un aspecto individual de la invención.

Se mencionan adicionalmente las realizaciones ($\underline{Hc}^5R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$) y ($\underline{Hc}^6R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$), con las características remanentes como se indica para los elementos de la matriz I.

a.) subconjunto de los aspectos 1 – 17 y realizaciones de la matriz 0 o I con respecto a R^2

(a.1.1) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en

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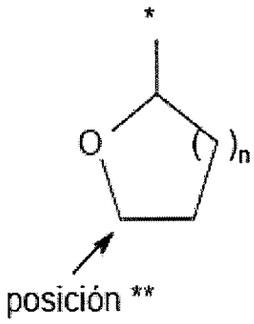
las que ***Hc*** dentro del grupo $\underline{Hc}[R^2]_x[R^3]_y$ puede ser un grupo definido por la siguiente fórmula D1

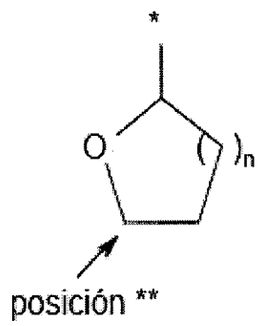


(D1),

en la que * es el punto de unión al grupo pirazolo en la fórmula general I y n = 0, 1, 2 o 3, excepto que en este subconjunto no hay para ninguna realización en la posición ** ningún R^2 que comprende un grupo $-CH_2-$ mediante el cual R^2 se une a dicha posición **:

Este subconjunto se denomina "subconjunto a.1.1".

(a.1.2) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** dentro del grupo $\underline{Hc}[R^2]_x[R^3]_y$ puede ser un grupo definido por la siguiente fórmula D1



(D1),

en la que * es el punto de unión al grupo pirazolo en la fórmula general I y n = 0, 1, 2 o 3; excepto que en este subconjunto no hay para ninguna realización en la posición ** ningún R^2 o R^3 distinto de H.

Este subconjunto se denomina "subconjunto a.1.2".

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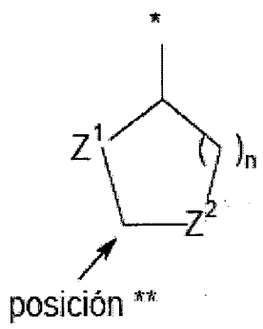
(a.2.1) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** dentro del grupo $\underline{Hc}[R^2]_x[R^3]_y$ puede ser un grupo definido por la siguiente fórmula D1-2



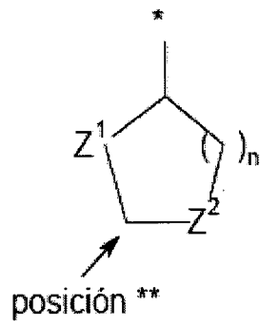
(D1-2),

en la que * es el punto de unión al grupo pirazolo en la fórmula general I y n = 1, 2 o 3 y en la que Z^1 se selecciona del grupo de N, O y $S(O)_r$, siendo r = 0, 1, 2 y Z^2 se selecciona del grupo de C, N, O y $S(O)_r$, siendo r = 0, 1, 2, en todos los casos con valencias eventualmente remanentes de Z^1 o Z^2 que son saturadas por H o según el caso por R^2 o R^3,

excepto que dentro de este subconjunto no hay para ninguna realización en la posición ** ningún R^2 que comprende un grupo $-CH_2-$ opcionalmente sustituido mediante el cual este R^2 se une a dicha posición **:

Este subconjunto se denomina “subconjunto a.2.1”.

(a.2.2) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que **Hc** dentro del grupo $Hc[R^2]_x[R^3]_y$ puede ser un grupo definido por la siguiente fórmula D1-2



(D1-2),

en la que * es el punto de unión al grupo pirazolo en la fórmula general I y n = 1, 2 o 3 y en la que Z^1 se selecciona del grupo de N, O y $S(O)_r$, siendo r = 0, 1, 2 y Z^2 se selecciona del grupo de C, N, O y $S(O)_r$, siendo r = 0, 1, 2, en todos los casos con valencias eventualmente remanentes de Z^1 o Z^2 que son saturadas por H o según el caso por R^2 o R^3,

excepto que dentro de este subconjunto no hay para ninguna realización en la posición ** ningún R^2 o R^3 distinto de H.

Este subconjunto se denomina "subconjunto a.2.2".

(a.3) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidrofuranilo, excepto que dentro de este subconjunto R^2 no es para ninguna realización un grupo CH_3 que se une en la posición alfa respecto al átomo de oxígeno del anillo.

Este subconjunto se denomina "subconjunto a.3".

(a.4) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidrofuranilo, excepto que dentro de este subconjunto R^2 no es para ninguna realización un grupo R^{10}-O-alquil C_{2-6}- que tiene un grupo CH_2- mediante el cual se une a un átomo de C del tetrahidrofuranilo, que está en la posición alfa respecto al átomo de oxígeno del anillo.

Este subconjunto se denomina "subconjunto a.4".

(a.5.1) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidrofuranilo, excepto que dentro de este subconjunto R^2 no es para ninguna realización un grupo alquil C_{1-6}- que se une en la posición alfa respecto al átomo de oxígeno del anillo.
Este subconjunto se denomina "subconjunto a.5.1".

(a.5.2) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidrofuranilo, excepto que dentro de este subconjunto R^2 no es para ninguna realización un grupo alquenil C_{2-6}- que se une en la posición alfa con respecto al átomo de oxígeno del anillo.
Este subconjunto se denomina "subconjunto a.5.2".

(a.5.3) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidrofuranilo, excepto que en este subconjunto R^2 no es para ninguna realización un grupo alquinil C_{2-6}- que se une en la posición alfa con respecto al átomo de oxígeno del anillo.
Este subconjunto se denomina "subconjunto a.5.3".

(a.6) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidrotiofenilo, excepto que en este subconjunto R^2 no es para ninguna realización un grupo CH_3 que se une en la posición alfa con respecto al átomo de azufre del anillo.
Este subconjunto se denomina "subconjunto a.6".

(a.7) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidrotiofenilo, excepto que en este subconjunto R^2 no es para ninguna realización un grupo R^{10}-O-alquil C_{2-6}- que tiene un grupo CH_2- mediante el cual se une a un átomo de C del tetrahidrotiofenilo, que está en la posición alfa con respecto al átomo de azufre del anillo.
Este subconjunto se denomina "subconjunto a.7".

(a.8) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidrotiofenilo, excepto que en este subconjunto R^2 no es para ninguna realización un grupo alquil C_{1-6}- que tiene un grupo CH_2- mediante el cual se une en la posición alfa con respecto al átomo de azufre del anillo.
Este subconjunto se denomina "subconjunto a.8".

(a.9) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidropiranilo o un tetrahidrotiopiranilo, excepto que en este subconjunto R^2 no es para ninguna realización un grupo CH_3 unido en la posición alfa con respecto al átomo de oxígeno del anillo o al átomo de azufre respectivamente.
Este subconjunto se denomina "subconjunto a.9".

(a.10) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidropiranilo o un tetrahidrotiopiranilo, excepto que en este subconjunto R^2 no es para ninguna realización un grupo R^{10}-O-alquil

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C_{2-6}- que tiene un grupo CH_2- mediante el cual se une a un átomo de C del tetrahidropiranilo o tetrahidrotiopiranilo cuyo átomo de C está en la posición alfa con respecto al átomo de oxígeno del anillo o al átomo de azufre respectivamente.

Este subconjunto se denomina "subconjunto a.10".

(a.11) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser tetrahidropiranilo o un tetrahidrotiopiranilo, excepto que en este subconjunto R^2 no es para ninguna realización un grupo alquil C_{1-6}- que tiene a grupo CH_2- mediante el cual se une en la posición alfa con respecto al átomo de oxígeno del anillo o al átomo de azufre respectivamente.

Este subconjunto se denomina "subconjunto a.11".

(a.12) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** puede ser un grupo oxetanilo, excepto que en este subconjunto para ninguna realización ***Hc*** es un grupo oxetanilo.

Este subconjunto se denomina "subconjunto a.12".

(a.13) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser un grupo de azúcar hexanosilo cíclico en el que para cualquiera de los grupos hidroxi el hidrógeno puede ser reemplazado opcionalmente por cualquier otro grupo y/o ***Hc*** es o puede ser un grupo de azúcar mono-desoxi o di-desoxi hexanosilo cíclico en el que para cualquiera de los grupos hidroxi remanentes el hidrógeno puede ser reemplazado opcionalmente por cualquier grupo, excepto que en este subconjunto R^2 no es

para ninguna realización un grupo CH_3 que se une en la posición alfa con respecto al átomo de oxígeno del anillo.
Este subconjunto se denomina "subconjunto a.13".

(a.14) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser un grupo de azúcar hexanosilo cíclico en el que para cualquiera de los grupos hidroxi el hidrógeno puede ser reemplazado opcionalmente por cualquier otro grupo y/o ***Hc*** es o puede ser un grupo de azúcar mono-desoxi o di-desoxi hexanosilo cíclico en el que para cualquiera de los grupos hidroxi remanentes el hidrógeno puede ser reemplazado opcionalmente por cualquier otro grupo, excepto que en este subconjunto R^2 no es para ninguna realización un grupo alquil C_{1-6} - que se une en la posición alfa con respecto al átomo de oxígeno del anillo.
Este subconjunto se denomina "subconjunto a.14".

(a.15) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 y matriz I en las que ***Hc*** es o puede ser un grupo de azúcar hexanosilo cíclico en el que para cualquiera de los grupos hidroxi el hidrógeno puede ser reemplazado opcionalmente por cualquier otro grupo y/o ***Hc*** es o puede ser un grupo de azúcar mono-desoxi o di-desoxi hexanosilo cíclico en el que para cualquiera de los grupos hidroxi remanentes el hidrógeno puede ser reemplazado opcionalmente por cualquier otro grupo, excepto que en este subconjunto R^2 no es para ninguna realización un grupo R^{10}-O-alquil C_{2-6}- que se une en la posición alfa con respecto al átomo de oxígeno del anillo.
Este subconjunto se denomina "subconjunto a.15".

(a.16) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada uno de los aspectos 1 – 17 y cada una de las realizaciones de la matriz 0 o I en las

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que R^2 se define de tal modo que puede comprender un grupo seleccionado entre $(R^{10})_2N$- y $(R^{10})_2N$-alquil C_{1-3}-, excepto que en este subconjunto para ninguna realización R^2 será $(R^{10})_2N$- o $(R^{10})_2N$-alquil C_{1-3}-, mientras que todas las definiciones restantes de R^2 permanecen sin cambios.

Este subconjunto se denomina "subconjunto a.16".

b.) subconjunto de realizaciones de la matriz 0 o de la matriz I con respecto a $R^{4/5}$

(b.1) En un subconjunto individual e independiente de realizaciones según la presente invención las realizaciones del mismo se corresponden con cada una de las realizaciones de la matriz 0 o de la matriz I en las que $\mathbf{R^{4/5}}$ es $\mathbf{R^{4/5.2}}$, donde para las realizaciones de este subconjunto

$\mathbf{R^{4/5.2-2}}$ significa que $\mathbf{R^4}$ y $\mathbf{R^5}$ independientemente uno de otro, son H- o flúor.

Este subconjunto se denomina "subconjunto b.1".

c.) subconjunto de realizaciones de la matriz I con respecto a R^{10}

(c.1) En un subconjunto individual e independiente de realizaciones según la presente invención se refiere a cada realización seleccionada del grupo de la matriz I siendo $\mathbf{R^{10}}$ definido por $\mathbf{R^{10.2}}$, $\mathbf{R^{10.3}}$ o $\mathbf{R^{10.4}}$: para las realizaciones de este subconjunto cada una de las definiciones $\mathbf{R^{10.2}}$, $\mathbf{R^{10.3}}$ y $\mathbf{R^{10.4}}$ se extiende de modo que $\mathbf{R^{10}}$ también puede ser H, en el caso en que este $\mathbf{R^{10}}$ se une a un átomo de nitrógeno.

Este subconjunto se denomina "subconjunto c.1".

Se pone de manifiesto que los subconjuntos como se definen en a.) y b.) dentro de esta sección "Realizaciones adicionales según la invención / subconjunto de los aspectos 1 – 17 y las realizaciones de la matriz 0 o de la matriz I" se corresponden con las realizaciones de los aspectos 1 – 17 y de la matriz 0, matriz I respectivamente, donde el alcance de las definiciones específicas se ha cambiado. En el caso en que estos cambios son limitaciones, se pueden considerar las nuevas definiciones para incluir condiciones. Por tanto estas realizaciones se consideran

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solamente como "subconjuntos" de los aspectos 1 – 17 y las realizaciones de la matriz 0 o de la matriz I respectivamente.

Cada realización de la fórmula general I definida por los aspectos 1 – 18 y cualquiera de los elementos de la matriz 0, matriz I, o cada realización definida por los subconjuntos anteriores a.), b.) o c.) se considera un aspecto independiente y separable de la invención, esto es, un aspecto individual de la invención.

TÉRMINOS Y DEFINICIONES UTILIZADOS

A los términos no definidos específicamente en esta memoria se les deben dar los significados que les daría una persona experta en la técnica a la vista de la descripción y del contexto. Los ejemplos incluyen los sustituyentes específicos o átomos que están presentes con sus códigos de 1 o 2 letras, como H para hidrógeno, N para nitrógeno, C para carbono, O para oxígeno, S para azufre y similares. Opcionalmente pero no obligatoriamente la letra va seguida por un guión para indicar un enlace. Tal como se utilizan en la memoria descriptiva, a menos que se especifique lo contrario, los siguientes términos tienen el significado indicado y se adhieren a los siguientes convenios.

En los grupos, radicales o restos que se definen a continuación, el número de átomos de carbono se especifica a menudo siguiendo al grupo, por ejemplo, alquilo C_{1-6} significa un grupo alquilo o radical alquilo que tiene 1 a 6 átomos de carbono. En general, para los grupos que comprenden dos o más subgrupos, el grupo mencionado en último lugar es el punto de fijación del radical, por ejemplo "tioalquilo" significa un radical monovalente de la fórmula HS-alquil-. Si el término de un sustituyente empieza o termina con un signo menos o con un guión, esto es, -. este signo indica el punto de unión como en el ejemplo mencionado antes HS-alquil-, en el que el "alquil" está unido al grupo del que el HS-alquil- es un sustituyente. A menos que se especifique de otro modo más adelante, las definiciones convencionales de los términos, control y valencias atómicas estables convencionales, se presumen y se establecen en todas las fórmulas y grupos.

En general, se proponen todas **"las formas tautoméricas y formas isoméricas y mezclas"**, ya sean isómeros geométricos o isómeros ópticos individuales o mezclas

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racémicas o no racémicas de isómeros, de una estructura o compuesto químico, a menos que en el nombre o estructura del compuesto se indique específicamente la estereoquímica específica o la forma isomérica.

El término "**sustituido**" tal como se utiliza en esta memoria explícita o implícitamente, significa que uno cualquiera o más hidrógenos sobre el átomo designado están reemplazados con un miembro del grupo indicado de sustituyentes, con la condición de que no se supere la valencia normal del átomo designado. En el caso en que un sustituyente se une mediante un doble enlace, p. ej. un sustituyente oxo, dicho sustituyente reemplaza a dos átomos de hidrógeno sobre el átomo designado. La sustitución producirá un compuesto estable. "Estable" en este contexto significa preferiblemente un compuesto que desde un punto de vista farmacéutico es química y físicamente suficientemente estable para ser utilizado como un ingrediente farmacéutico activo de una composición farmacéutica. Si un sustituyente no está definido, será hidrógeno.

Por el término "**opcionalmente sustituido**" se indica que el grupo correspondiente está sustituido o no lo está. Por consiguiente, en cada ocasión en que se utiliza este término, la variación no sustituida es un aspecto más acusado de la invención, esto es, preferiblemente no hay tales sustituyentes opcionales.

La frase "**farmacéuticamente aceptable**" se emplea en esta memoria para hacer referencia a los compuestos, materiales, composiciones y/o formas farmacéuticas que, basándose en el buen criterio médico, son adecuados para el uso en contacto con los tejidos de los seres humanos y animales sin una toxicidad, irritación o respuesta alérgica excesivas, ni ningún otro problema o complicación, acorde con una relación beneficio/riesgo razonable.

Tal como se utiliza en esta memoria, "**sales farmacéuticamente aceptables**" se refieren a derivados de los compuestos descritos, en los que el compuesto original se modifica preparando sales de ácidos o bases del mismo. Ejemplos de sales farmacéuticamente aceptables incluyen, pero sin limitarse a ellas, sales de ácidos minerales u orgánicos de restos de carácter básico, tales como aminas; sales alcalinas u orgánicas de restos de carácter ácido, tales como ácidos carboxílicos; y

similares. Las sales farmacéuticamente aceptables incluyen las sales no tóxicas convencionales o las sales de amonio cuaternario del compuesto parental, formadas por ejemplo a partir de ácidos inorgánicos u orgánicos no tóxicos. Por ejemplo, las sales no tóxicas convencionales de este tipo incluyen las derivadas de ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido sulfámico, ácido fosfórico, ácido nítrico y similares; y las sales preparadas a partir de ácidos orgánicos, tales como ácido acético, ácido propiónico, ácido succínico, ácido glicólico, ácido esteárico, ácido láctico, ácido málico, ácido tartárico, ácido cítrico, ácido ascórbico, ácido pamoico, ácido maleico, ácido hidroximaleico, ácido fenilacético, ácido glutámico, ácido benzoico, ácido salicílico, ácido sulfanílico, ácido 2-acetoxibenzoico, ácido fumárico, ácido toluenosulfónico, ácido metanosulfónico, ácido etanodisulfónico, ácido oxálico, ácido isotiónico, y similares. Como los compuestos de la presente invención pueden tener tanto grupos ácidos como grupos básicos, estos compuestos pueden estar presentes por tanto también como sales internas.

Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir del compuesto original que contiene un resto básico o ácido por métodos químicos convencionales. En general, las sales de este tipo se pueden preparar haciendo reaccionar la forma de ácido o base libre de estos compuestos con una cantidad estequiométrica de la base o el ácido apropiado en agua o en un disolvente orgánico, o en una mezcla de los dos; en general, se prefieren medios no acuosos tales como éter, acetato de etilo, etanol, isopropanol o acetonitrilo.

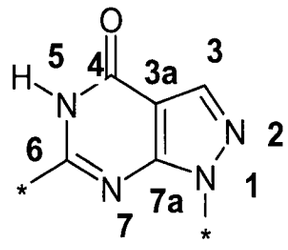
Se consideran "**profármacos**" los compuestos que liberan un fármaco parental activo de la presente invención *in vivo* cuando dicho profármaco es administrado a un mamífero. Los profármacos según la presente invención se preparan modificando los grupos funcionales presentes en el compuesto de tal modo que estas modificaciones se transforman después en los grupos funcionales originales en condiciones fisiológicas. Los profármacos incluyen los compuestos de la presente invención en los que un grupo hidroxi, amino o sulfhidrilo está unido a cualquier grupo que, cuando se administra el profármaco de la presente invención a un mamífero, se transforma después para liberar dicho grupo hidroxilo, amino o sulfhidrilo. Los ejemplos de profármacos incluyen, pero sin limitarse a ellos,

derivados acetato, formiato y benzoato de grupos funcionales alcohol y amina de los compuestos de la presente invención.

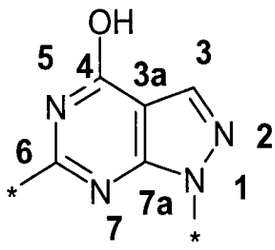
Los "**metabolitos**" se consideran como derivados de los compuestos según la presente invención que se forman *in vivo*. Son metabolitos activos los metabolitos que producen un efecto farmacológico. Se deberá apreciar que los metabolitos de los compuestos según las actuales invenciones corresponden también a la presente invención, en particular los metabolitos activos.

Algunos de los compuestos pueden formar "**solvatos**". Para los fines de la invención, el término "solvatos" se refiere a aquellas formas de los compuestos que forman, en estado sólido o líquido, un complejo por coordinación con las moléculas de disolvente. Los hidratos son una forma específica de solvatos en los que tiene lugar la coordinación con agua. Según la presente invención, el término se usa preferiblemente para los solvatos sólidos, tales como los solvatos amorfos o más preferiblemente cristalinos.

"**Scaffold**": El scaffold (estructura química) de los compuestos según la presente invención se representa por el siguiente núcleo estructural, cuya numeración se indica en negrita:

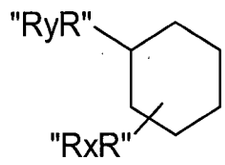


Será evidente para las personas expertas en la técnica, que esta estructura química se puede describir por su forma tautomérica "enol"



En el contexto de la presente invención ambas representaciones estructurales del scaffold se deben considerar objeto de la presente invención, incluso cuando se presenta sólo uno de los dos representantes. Se cree que para la mayoría de los compuestos en condiciones ambientales y en condiciones que son condiciones relevantes para una composición farmacéutica que comprende dichos compuestos, el equilibrio de las formas tautómeras está en el lado de la representación de la pirazolopirimidin-4-ona. Por tanto, todas las realizaciones se presentan como derivados de pirazolopirimidin-4-ona o más precisamente como derivados de pirazolo[3,4-d]pirimidin-4-ona.

"**Enlaces**": Si dentro de una fórmula química de un sistema de anillos o de un grupo definido, un sustituyente está directamente ligado a un átomo o a un grupo tipo "RyR" en la fórmula que sigue, esto significa que el sustituyente está unido solamente al átomo correspondiente. Sin embargo, si a partir de otro sustituyente como RxR no hay un enlace específicamente ligado a un átomo del sistema de anillos sino dirigido hacia el centro del anillo o grupo, esto significa que este sustituyente "RxR" puede estar ligado a cualquier átomo importante del sistema de anillos/grupo a menos que se indique otra cosa.



El símbolo de enlace "-" (= signo menos) o el símbolo "- *" (= signo menos seguido por un asterisco) significa el enlace mediante el cual un sustituyente se une a la correspondiente parte restante de la molécula/estructura. En los casos en que el

signo menos no parece estar suficientemente claro, se añade un asterisco al símbolo del enlace "-" con el fin de determinar el punto de unión de dicho enlace con la correspondiente parte principal de la molécula/estructura.

En general, el enlace a uno de los grupos heterocicloalquilo, heterociclilo o heteroarilo definidos aquí, se puede efectuar mediante un átomo de C u opcionalmente mediante un átomo de N.

El término "**arilo**" usado en esta solicitud indica un grupo fenilo, bifenilo, indanilo, indenilo, 1,2,3,4-tetrahidronaftilo o naftilo, preferiblemente indica un grupo fenilo o naftilo, más preferiblemente un grupo fenilo. Esta definición se aplica al uso de "**arilo**" en cualquier contexto dentro de la presente descripción en ausencia de una definición adicional.

El término "**alquilo C_{1-n}**" indica un grupo hidrocarbonado saturado, ramificado o no ramificado con 1 a n átomos de C, en el que n es un número seleccionado del grupo de 2, 3, 4, 5, 6, 7, 8, 9, o 10, preferiblemente del grupo de 2, 3, 4, 5, o 6, más preferiblemente del grupo de 2, 3, o 4. Ejemplos de tales grupos incluyen metilo, etilo, *n*-propilo, *iso*-propilo, butilo, *iso*-butilo, *sec*-butilo, *terc*-butilo, *n*-pentilo, *iso*-pentilo, *neo*-pentilo, *terc*-pentilo, *n*-hexilo, *iso*-hexilo etc. Como se pone de manifiesto en el contexto, dicho grupo **alquilo C_{1-n}** puede estar opcionalmente sustituido.
Esta definición se aplica al uso de "**alquilo**" en cualquier contexto razonable dentro de la presente descripción en ausencia de una definición adicional.
En los casos en que el término "**alquilo C_{1-n}**" se usa en medio de otros dos grupos / sustituyentes, como por ejemplo en **"cicloalquil C_{1-n}-alquil C_{1-n}-O-"**, esto significa que el resto "alquilo C_{1-n}" hace de puente entre los otros dos grupos. En el presente ejemplo hace de puente entre el cicloalquilo C_{1-n} y el oxígeno como en "ciclopropil-metil-oxi-". Será evidente, que en tales casos el "alquilo C1-n" tiene el significado de un separador "alquileno C1-n" como metileno, etileno etc. Los grupos que están separados por el puente "alquilo C1-n" pueden estar unidos a "alquilo C1-n" en cualquier posición del mismo. Preferiblemente el grupo del lado derecho está localizado en el extremo distal derecho del grupo alquilo y el grupo del lado izquierdo en el lado distal izquierdo del grupo alquilo. Lo mismo se aplica a otros sustituyentes.

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El término "**alquenilo C_{2-n}**" indica un grupo hidrocarbonado ramificado o no ramificado con 2 a n átomos de C y al menos un doble enlace C=C (esto es, doble enlace carbono – carbono), en el que n tiene preferiblemente un valor seleccionado del grupo de 3, 4, 5, 6, 7, u 8, más preferiblemente 3, 4, 5, o 6, más preferiblemente 3 o 4. Ejemplos de tales grupos incluyen etenilo, 1-propenilo, 2-propenilo, *iso*-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 2-metil-1-propenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 3-metil-2-butenilo, 1-hexenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo etc. Como queda claro desde el contexto, dicho grupo **alquenilo C_{2-n}** puede estar opcionalmente sustituido.

Esta definición se aplica al uso de "**alquenilo**" en cualquier contexto razonable dentro de la presente descripción en ausencia de una definición adicional si no hay otra definición.

En los casos en que el término "**alquenilo C_{2-n}**" se usa en medio de otros dos grupos / sustituyentes, se aplica una definición análoga a la del alquilo C_{1-n}.

El término "**alquinilo C_{2-n}**" indica un grupo hidrocarbonado ramificado o no ramificado con 2 a n átomos de C y al menos un grupo C≡C (esto es, un triple enlace carbono-carbono), en el que n tiene preferiblemente un valor seleccionado del grupo de 3, 4, 5, 6, 7, u 8, más preferiblemente 3, 4, 5, o 6, más preferiblemente 3 o 4. Ejemplos de tales grupos incluyen etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo etc. Como queda claro desde el contexto, d**icho** grupo **alquinilo C_{2-n}** puede estar opcionalmente sustituido.

Esta definición se aplica al uso de "**alquinilo**" en cualquier contexto razonable dentro de la presente descripción en ausencia de una definición adicional.

En los casos en que el término "**alquinilo C_{2-n}**" se usa en medio de otros dos grupos / sustituyentes, se aplica una definición análoga a la del alquilo C_{1-n}.

El término "**cicloalquilo C_{3-n}**" indica un grupo monocíclico saturado con 3 a n átomos de C. n tiene preferiblemente un valor de 4 a 8 (= 4, 5, 6, 7, u 8), más

preferiblemente 4 a 7, más preferiblemente dicho cicloalquilo C_{3-n} tiene 5 o 6 miembros. Ejemplos de tales grupos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, etc. Esta definición se aplica para "**cicloalquilo**" en cualquier contexto razonable dentro de la presente descripción en ausencia de una definición adicional.

El término "**halógeno**" indica un átomo seleccionado entre F, Cl, Br y I.

El término "**heteroarilo**" usado en esta solicitud indica un sistema de anillos aromático heterocíclico, mono- o bicíclico que incluye dentro del propio sistema de anillos en adición a al menos un átomo de C, uno o más heteroátomos seleccionados independientemente de N, O, y/o S. Un sistema de anillos monocíclico consta preferiblemente de 5 a 6 miembros en el anillo, un sistema de anillos bicíclico consta preferiblemente de 8 a 10 miembros en el anillo. Se prefieren los heteroarilos con hasta 3 heteroátomos, más preferiblemente hasta 2 heteroátomos, más preferiblemente con 1 heteroátomo. El heteroátomo preferido es N. Ejemplos de tales restos son bencimidazolilo, bencisoxazolilo, benzo[1,4]-oxazinilo, benzoxazol-2-onilo, benzofuranilo, benzoisotiazolilo, 1,3-benzodioxolilo, benzotiadiazolilo, benzotiazolilo, benzotienilo, benzoxadiazolilo, benzoxazolilo, cromanilo, cromenilo, cromonilo, cinolinilo, 2,3-dihidrobenzo[1,4]dioxinilo, 2,3-dihidrobenzofuranilo, 3,4-dihidrobenzo[1,4]oxazinilo, 2,3-dihidroindolilo, 1,3-dihidroisobenzofuranilo, 2,3-dihidroisoindolilo, 6,7-dihidropirrolizinilo, dihidroquinolin-2-onilo, dihidroquinolin-4-onilo, furanilo, imidazo[1,2-*a*]pirazinilo, imidazo[1,2-*a*]piridilo, imidazolilo, imidazopiridilo, imidazo[4,5-d]tiazolilo, indazolilo, indolizinilo, indolilo, isobenzofuranilo, isobenzotienilo, isocromanilo, isocromenilo, isoindoilo, isoquinolin-2-onilo, isoquinolinilo, isotiazolilo, isoxazolilo, naftiridinilo, 1,2,4-oxadiazoilo, 1,3,4-oxadiazoilo, 1,2,5-oxadiazoilo, oxazolopiridilo, oxazolilo, 2-oxo-2,3-dihidrobencimidazolilo, 2-oxo-2,3-dihidroindolilo, 1-oxoindanilo, ftalazinilo, pteridinilo, purinilo, pirazinilo, pirazolo[1,5-*a*]piridilo, pirazolo[1,5-*a*]pirimidinilo, pirazolilo, piridazinilo, piridopirimidinilo, piridilo (piridinilo), piridil-*N*-óxido, pirimidinilo, pirimidopirimidinilo, pirrolopiridilo, pirrolopirimidinilo, pirrolilo, quinazolinilo, quinolin-4-onilo, quinolinilo, quinoxalinilo, 1,2,3,4-tetrahidroquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, tetrazolilo, 1,2,4-tiadiazolilo, 1,3,4-tiadiazolilo, 1,2,5-

tiadiazolilo, tiazolilo, tieno[2,3-*d*]imidazolilo, tieno[3,2-*b*]pirrolilo, tieno[3,2-*b*]tiofenilo, tienilo, triazinilo, o triazolilo.

Los grupos heteroarilo preferidos son furanilo, isoxazolilo, pirazolilo, piridilo, pirimidinilo, tienilo, y tiazolilo.

Los grupos heteroarilo más preferidos son oxadiazolilo, triazolilo, pirazolilo, furanilo, y piridilo, los más preferidos son pirazolilo y piridilo.

La definición de pirazol incluye los isómeros 1H-, 3H- y 4H-pirazol. Preferiblemente pirazolilo indica 1H-pirazolilo.

La definición de imidazol incluye los isómeros 1H-, 2H- y 4H-imidazol. Una definición preferida de imidazolilo es 1H-imidazolilo.

La definición de triazol incluye los isómeros 1H-, 3H- y 4H-[1,2,4]-triazol así como 1H-, 2H- y 4H-[1,2,3]-triazol. La definición de triazolilo incluye por tanto 1H-[1,2,4]-triazol-1-, -3- y -5-ilo, 3H-[1,2,4]-triazol-3- y -5-ilo, 4H-[1,2,4]-triazol-3-, -4- y -5-ilo, 1H-[1,2,3]-triazol-1-, -4- y -5-ilo, 2H-[1,2,3]-triazol-2-, -4- y -5-ilo así como 4H-[1,2,3]-triazol-4- y -5-ilo.

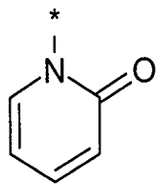
El término tetrazol incluye los isómeros 1H-, 2H- y 5H-tetrazol. La definición de tetrazolilo incluye por tanto 1H-tetrazol-1- y -5-ilo, 2H-tetrazol-2- y -5-ilo y 5H-tetrazol-5-ilo.

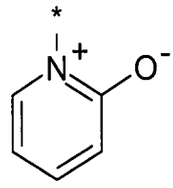
La definición de indol incluye los isómeros 1H- y 3H-indol. El término indolilo indica preferiblemente 1H-indol-1-ilo.

El término isoindol incluye los isómeros 1H- y 2H-isoindol.

Esta definición se aplica para "**heteroarilo**" en cualquier contexto razonable dentro de la presente descripción en ausencia de una definición adicional.

El término "**piridin-2-ona unida por el N** " usado en esta solicitud indica:



y su forma tautómera  .

El término "**heterocicloalquilo**" dentro del contexto de la presente invención indica un sistema de anillos saturado de 3 a 8 miembros, preferiblemente de 5, 6 o 7 miembros o un sistema de anillos bicíclico de 5-12 miembros, que incluye 1, 2, 3 o 4 heteroátomos, seleccionado entre N, O, y/o S. Lo preferido son 1, 2, o 3 heteroátomos.

El número preferido de átomos de carbono es 3 a 7 con 1, 2, 3 o 4 heteroátomos seleccionados entre N, O, y/o S. Tales grupos heterocicloalquilo son tratados como heterocicloalquilo C_{3-7}.

Los anillos de heterocicloalquilo preferidos son saturados con 5, 6, o 7 átomos en el anillo, de los cuales 1 o 2 son heteroátomos y los restantes son átomos de C.

Siempre que se mencionan los sustituyentes heterocicloalquil C_{3-7}-, las realizaciones preferidas de los mismos son ciclos de 5, 6 o 7 miembros, más preferiblemente monociclos. Ellos incluyen 1, 2, 3, o 4 heteroátomos, seleccionados entre N, O, y/o S, donde se prefieren 1 o 2 de tales heteroátomos, más preferiblemente 1 de tales heteroátomos.

Los ejemplos preferidos de heterocicloalquilo incluyen los grupos morfolinilo, piperidinilo, piperazinilo, tiomorfolinilo, oxatianilo, ditianilo, dioxanilo, pirrolidinilo, tetrahidrofuranilo, dioxolanilo, oxatiolanilo, imidazolidinilo, tetrahidropiranilo, pirrolinilo, tetrahidrotienilo, oxazolidinilo, homopiperazinilo, homopiperidinilo, homomorfolinilo, homotiomorfolinilo, azetidinilo, 1,3-diazaciclohexanilo o pirazolidinilo.

Esta definición se aplica para "**heterocicloalquilo**" en cualquier contexto razonable dentro de la presente descripción en ausencia de una definición específica adicional.

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

Organizacion y Digitalizacion CSA Ltda

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-121065

3/3

54. **TÍTULO** _____

_____

_____

_____

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** _____

DOMICILIO _____

74. **APODERADO** _____

22. **BOGOTÁ, D.C.,** _____

(FORMA P-10)

El término "**heterociclilo**" se usa específicamente para definir el grupo ***Hc*** en la fórmula I y en las fórmulas que se derivan de la misma y por tanto se utilizará independientemente de la definición de "heterocicloalquilo". Sin embargo, las definiciones para "heterocicloalquilo" deben estar comprendidas dentro de la definición de "heterociclilo". ***Hc*** es un grupo que es o al menos comprende un grupo heterocicloalquilo no aromático que se une a la estructura química (scaffold).

Dentro del contexto de la presente invención y como se usa en esta memoria, específicamente dentro del contexto de ***Hc***, "**heterociclilo**" significa un sistema de anillos no aromáticos monocíclico, bicíclico o tricíclico, donde los miembros del anillo son átomos de carbono y al menos uno, preferiblemente uno a tres heteroátomos seleccionados del grupo de nitrógeno, oxígeno, o azufre, formando el azufre parte del grupo $-S(O)_r$ - siendo r 0, 1 o 2. Tal sistema de anillos puede tener además un puente. Dichos sistemas se denominan también sistema de anillos heteromonocíclicos, heterobicíclicos, o heterotricíclicos dentro del presente contexto.

Este grupo heterociclilo puede ser saturado o parcialmente insaturado, y en los sistemas con más de un sistema de anillos, al menos uno de ellos no es aromático. Éste, al menos un sistema de anillos no aromático, comprende dicho al menos un, heteroátomo.

Este grupo heterociclilo puede estar unido a la estructura química (scaffold) de más de una manera. Si no se especifica ninguna disposición particular de enlace, entonces se intentan todas las posibles disposiciones. Por ejemplo, el término "tetrahidropiranilo" incluye 2-, 3-, o 4- tetrahidropiranilo y similares. En los casos con más de un sistema de anillos, el enlace a la estructura química es mediante al menos un átomo del anillo del sistema de anillos no aromático que comprende al menos un heteroátomo. Preferiblemente este grupo heterociclilo se une a la estructura química mediante un átomo de nitrógeno o uno de los átomos de carbono saturados en dicho sistema de anillos. Más preferiblemente se une a la estructura química mediante un átomo de carbono del sistema de anillos heterocíclico no aromático.

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Dicho grupo heterociclilo puede estar condensado, anillado respectivamente, con un cicloalquilo, otro grupo heterocíclico, un sistema de anillos aromático, tal como fenilo o puede formar parte de un sistema espirocíclico. En un sistema condensado o anillado, los dos sistemas de anillos comparten un enlace entre dos átomos adyacentes del anillo. En la variación espiro, los dos sistemas de anillos tienen en común un átomo del anillo.

Los sistemas de anillos monoheterocíclicos dentro de esta definición son sistemas de anillos monocíclicos no aromáticos, en los que al menos uno, preferiblemente uno a tres, de los átomos de carbono han sido reemplazados con un heteroátomo tal como nitrógeno, oxígeno, o azufre, formando el azufre parte del grupo – $S(O)_r$ - siendo r 0, 1 o 2, comprenden preferiblemente 4 a 8 átomos en el anillo. Dentro de este contexto son preferidos los anillos heterocíclicos, saturados o al menos parcialmente insaturados, de 5, 6 o 7 miembros

Los sistemas de anillos heterobicíclicos dentro de esta definición son sistemas de anillos bicíclicos en los que al menos uno, preferiblemente uno a tres, de los átomos de carbono han sido reemplazados con un heteroátomo tal como nitrógeno, oxígeno, o azufre, formando el azufre parte del grupo – $S(O)_r$ - siendo r 0, 1 o 2; el sistema de anillos tiene al menos un anillo no aromático, que comprende dicho al menos un heteroátomo, y el sistema de anillos bicíclico comprende preferiblemente 7 a 12 átomos en el anillo. Dentro de este contexto son preferidos los anillos heterocíclicos, saturados o al menos parcialmente insaturados, de 8, 9 o 10 miembros

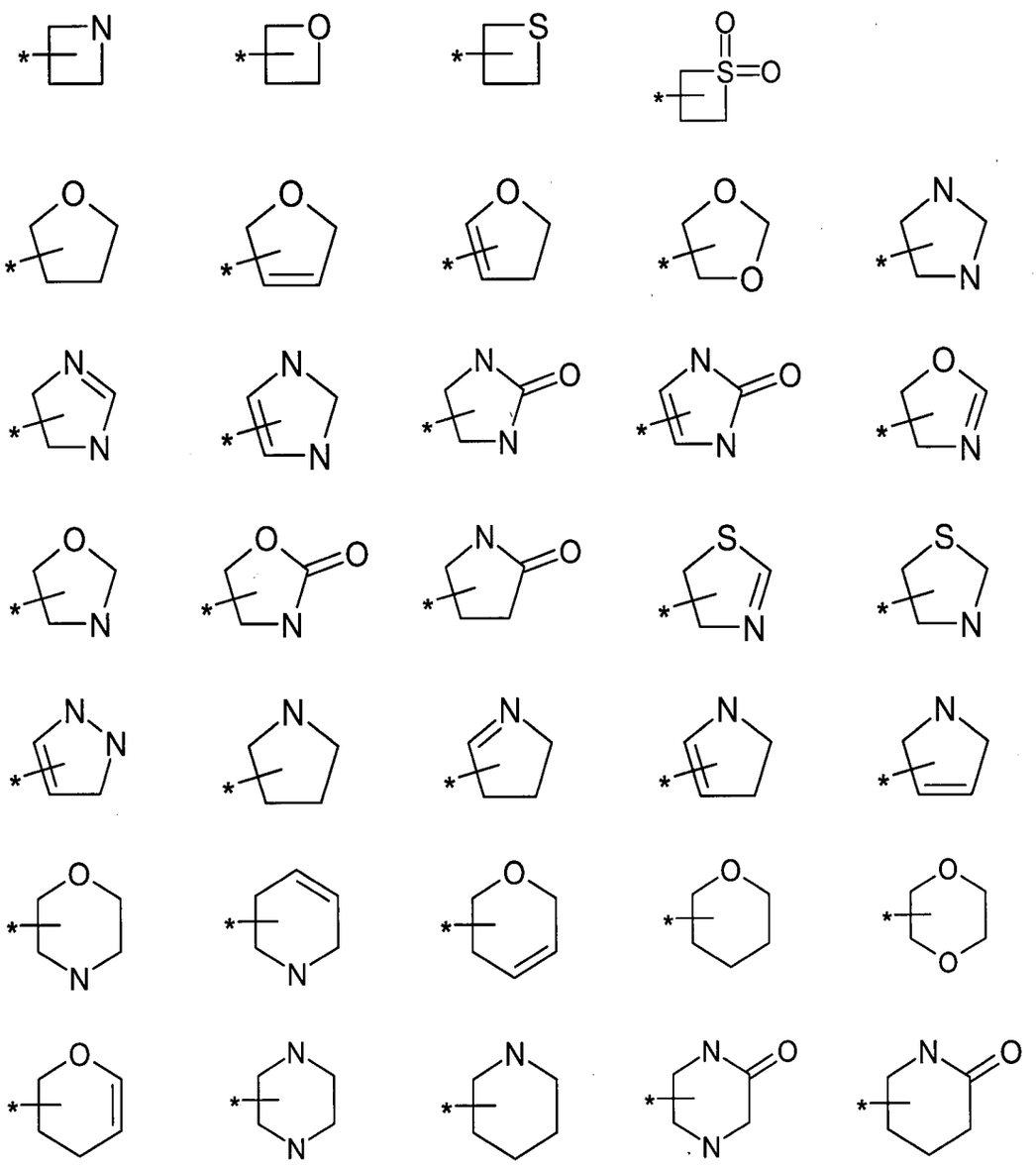
Los sistemas de anillos heterotricíclicos dentro de esta definición son sistemas de anillos tricíclicos de monociclos anillados, en los que al menos uno, preferiblemente uno a tres, de los átomos de carbono han sido reemplazados con un heteroátomo tal como nitrógeno, oxígeno, o azufre, formando el azufre parte del grupo – $S(O)_r$ - siendo r 0, 1 o 2; el sistema de anillos tiene al menos un anillo no aromático, que comprende dicho al menos un heteroátomo, y el sistema de anillos tricíclico comprende preferiblemente 7 a 14 átomos en el anillo.

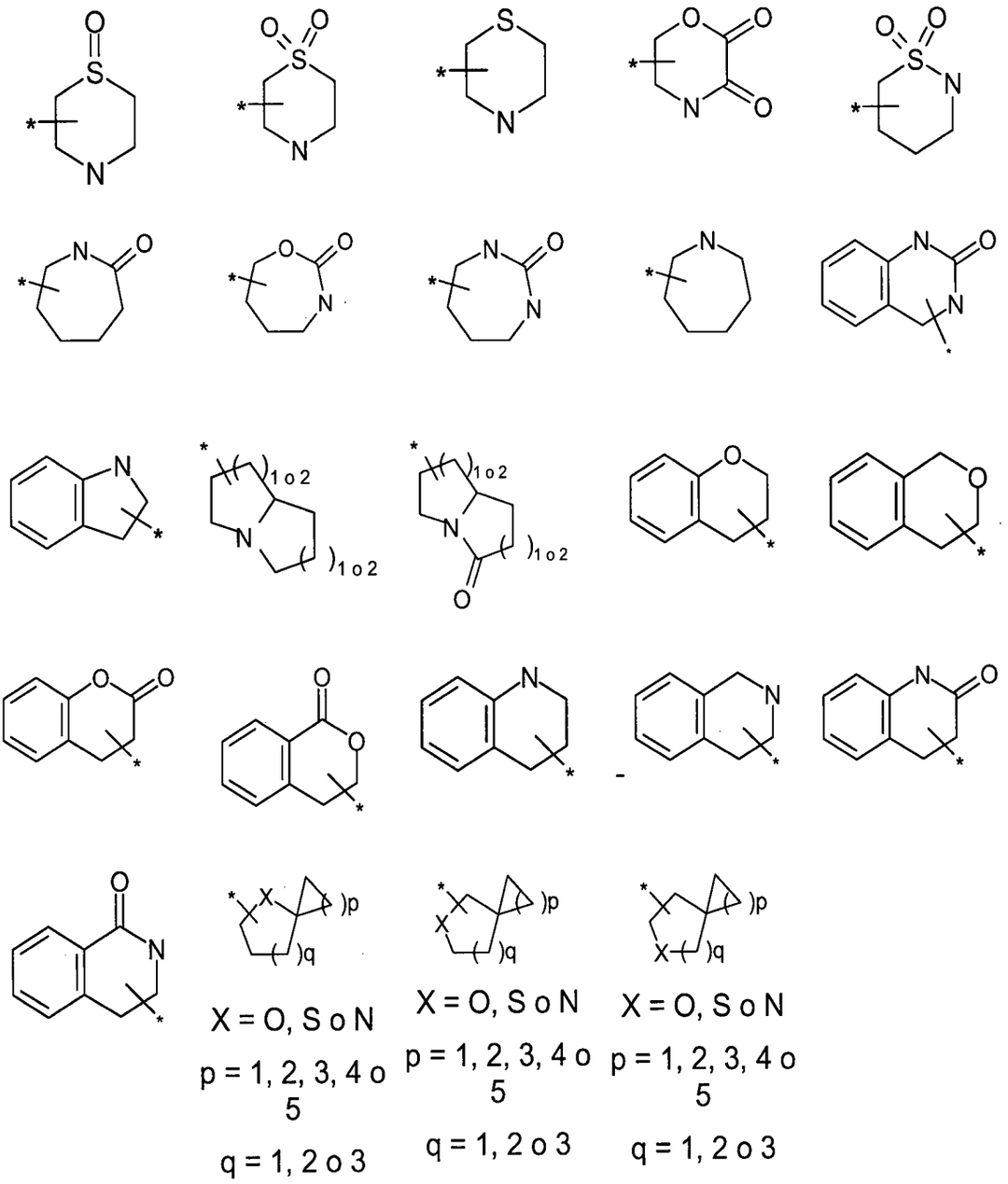
Por el término sistema espirocíclico como se menciona dentro de esta definición, se indican preferiblemente anillos espirocíclicos de 5-10 miembros, que pueden

contener opcionalmente 1, 2 o 3 heteroátomos, seleccionados entre oxígeno, azufre, y nitrógeno. Tales sistemas pueden estar opcionalmente anillados con un sistema de anillo aromático tal como fenilo.

El orden de preferencia de los sistemas de anillos heterocíclicos es: los sistemas de anillos monocíclicos son más preferidos que los sistemas de anillos bicíclicos, que son más preferidos que los tricíclicos.

Ejemplos de tales grupos heterocíclicos ***Hc*** según la presente invención son los siguientes grupos:





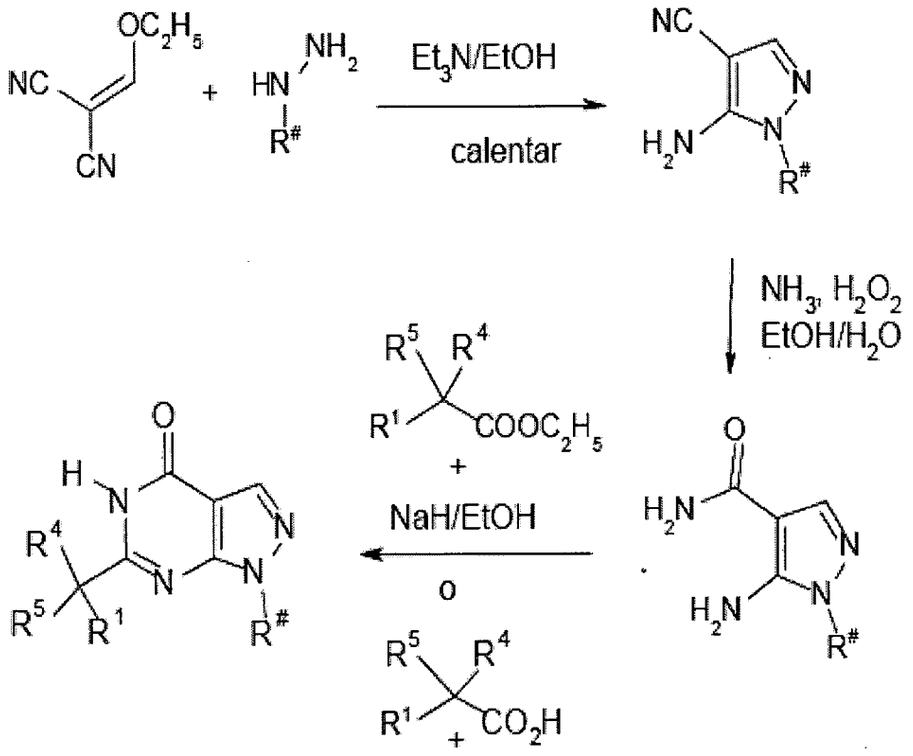
donde -* indica el enlace mediante el cual dicho grupo se une al átomo de nitrógeno de la estructura química, que se numera como 1.

La definición anterior se aplica para "**heterociclilo**" en cualquier contexto razonable dentro de la presente descripción en ausencia de una definición adicional.

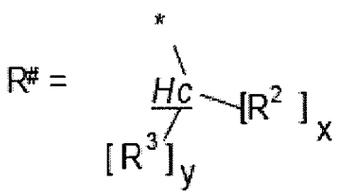
El término "**oxo**" indica un átomo de oxígeno como sustituyente que se enlaza mediante un doble enlace, preferiblemente se enlaza a un átomo de C. En el caso en que oxo se usa como un sustituyente, oxo reemplaza a dos átomos de hidrógeno del correspondiente átomo del compuesto no sustituido.

Los siguientes esquemas ilustran un procedimiento para fabricar los compuestos de la presente invención, a modo de ejemplo:

Esquema 1



con



Esquema 1: En una primera etapa se condensa 2-etoximetilen-malononitrilo con hidrazinas monosustituidas calentando en un disolvente apropiado tal como etanol en presencia de una base (p. ej. trietilamina) para formar 5-amino-1H-pirazol-4-carbonitrilos. Estos compuestos se convierten en una segunda etapa en las correspondientes amidas, p. ej. por tratamiento de una solución etanólica con amoníaco (al 25 % en agua) y peróxido de hidrógeno (al 35 % en agua). En una tercera etapa, calentando con ésteres carboxílicos en condiciones básicas (p. ej. hidruro de sodio en etanol) o ácidos carboxílicos con un reactivo de activación (p. ej.

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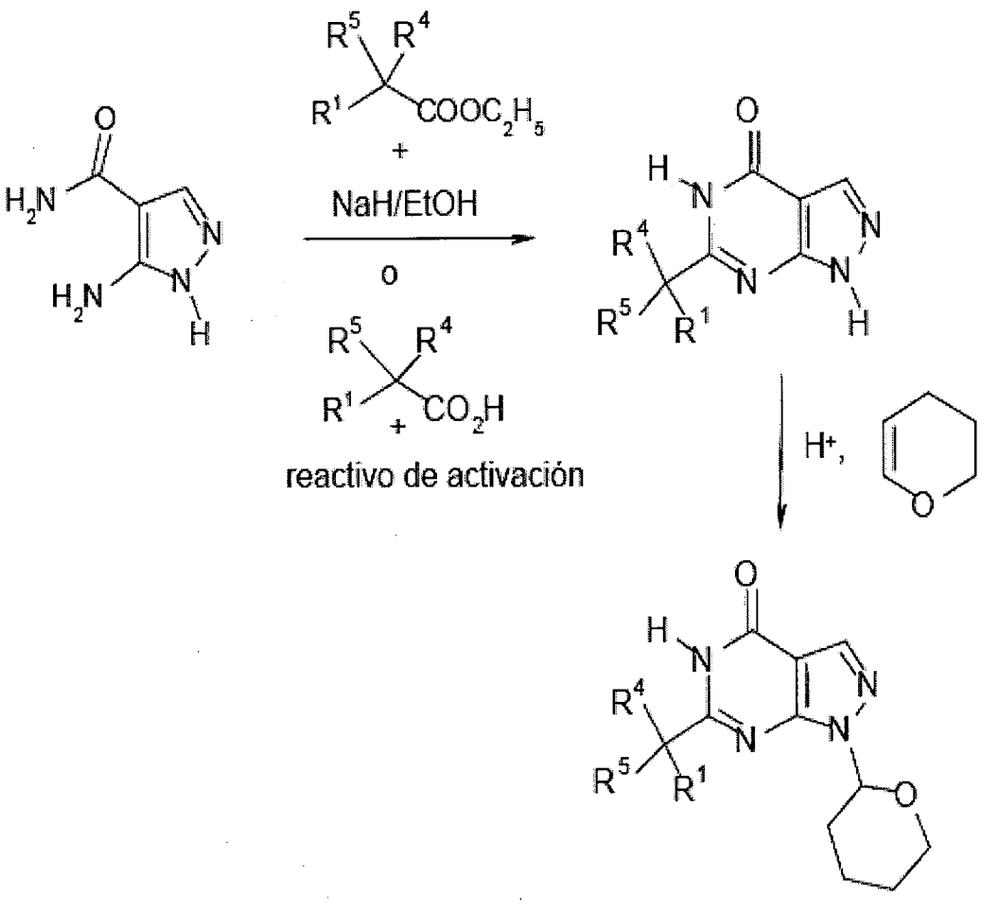
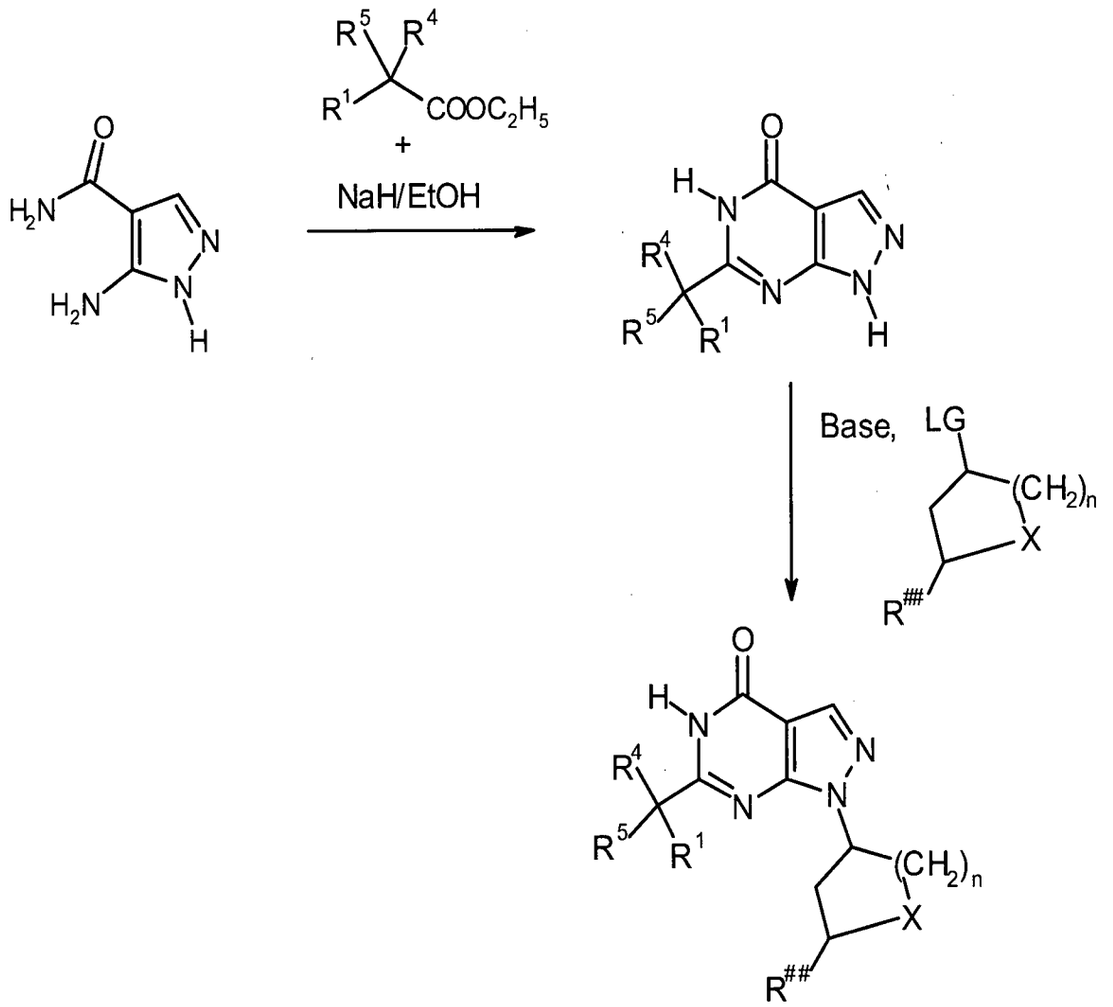
ácido polifosfórico) se llega a las pirazolo[3,4-d]pirimidin-4-onas como productos finales [véase, por ejemplo, A. Miyashita *et al.*, *Heterocycles* **1990**, *31*, 1309ff].

Los esquemas 2 y 3 ilustran métodos alternativos para preparar los compuestos finales: en estos ejemplos de métodos de fabricación las amidas del ácido 5-amino-1H-pirazol-4-carboxílico se condensan en una primera etapa con un derivado de éster apropiado seguido en una segunda etapa por alquilación con electrófilos adecuados.

Esquema 2



Esquema 3



X = O, NH, NR^2, S, SO o SO_2

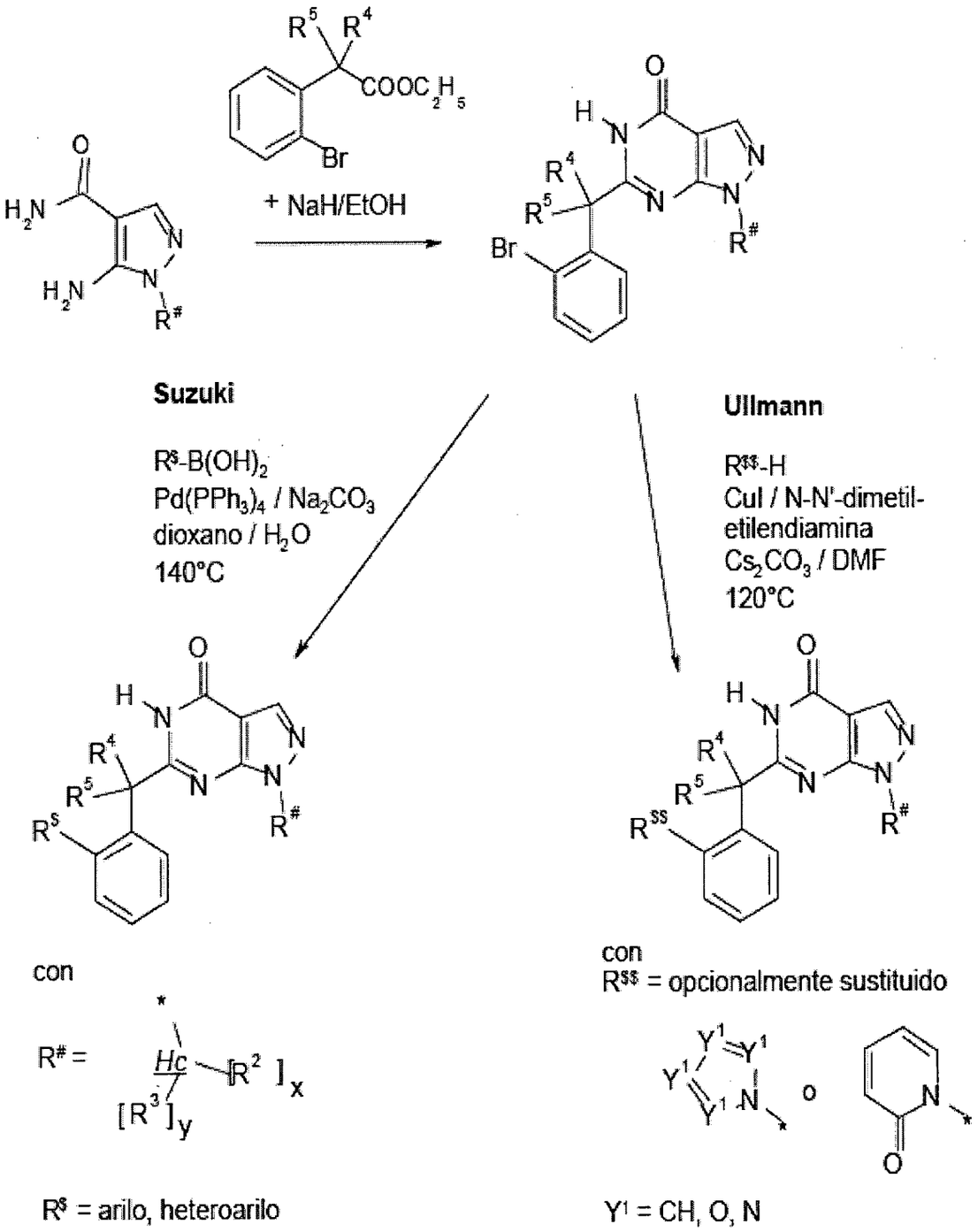
$R^{\#\#} = R^2$ o R^3

LG = Br-, Cl-, I-, CH_3-SO_2-O-, p-toluenosulfonil-

n = 1,2

El Esquema 4 ilustra métodos alternativos para preparar los compuestos finales: en los ejemplos de métodos de fabricación las amidas del ácido 5-amino-1H-pirazol-4-carboxílico se condensan en una primera etapa con derivados de éster de ácido (2-bromo-fenil)-acético seguido en una segunda etapa por sustitución del átomo de bromo por un residuo aromático o heteroaromático, p. ej. utilizando las condiciones de reacción tipo Suzuki o Ullmann.

Esquema 4



El Esquema 5 ilustra un método alternativo para preparar los compuestos finales: en los ejemplos del método de fabricación las amidas del ácido 5-amino-1H-pirazol-4-carboxílico se condensan en una primera etapa con derivados de éster de ácido (2-ciano-fenil)-acético seguido en una segunda etapa por transformación del grupo nitrilo en un grupo heteroaromático de 5 miembros.

Esquema 5

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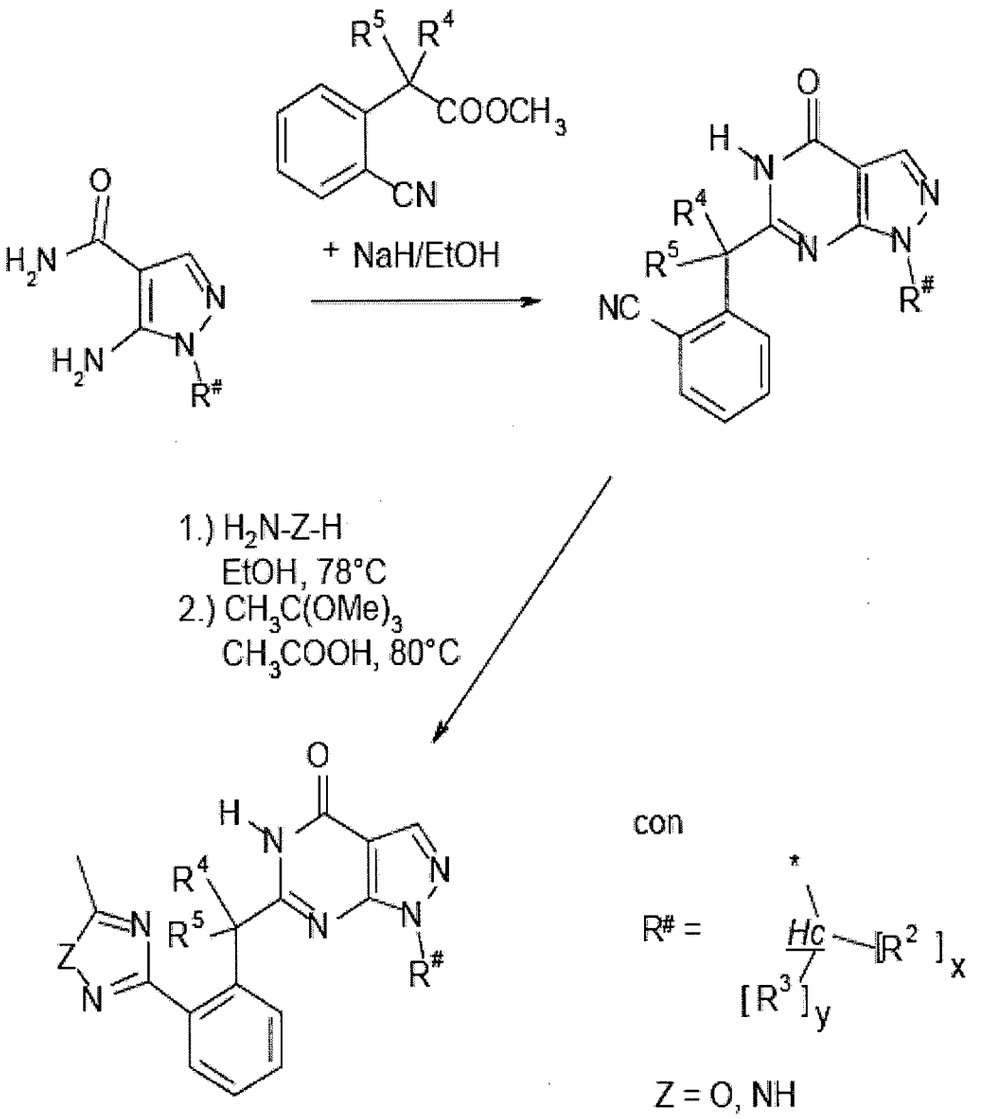
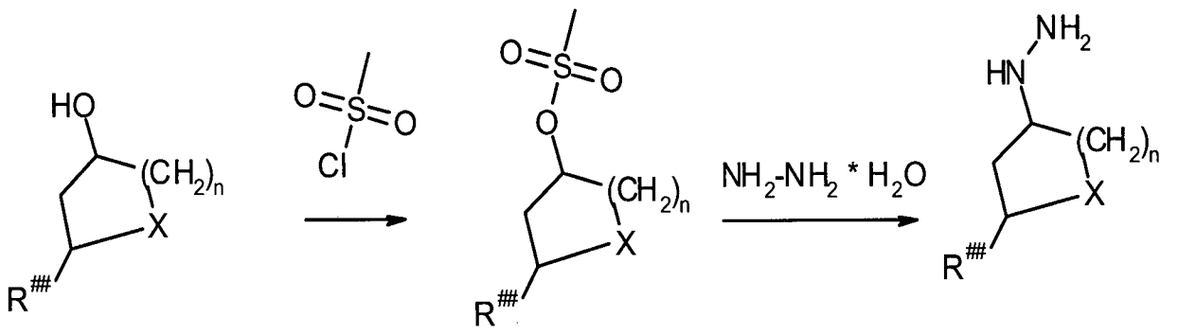


Se conocen en la técnica otros procedimientos alternativos para preparar pirazolo[3,4-d]pirimidin-4-onas y se pueden emplear a su vez para sintetizar los compuestos de la invención (véase, por ejemplo: P. Schmidt *et al.*, *Helvetica Chimica Acta* **1962**, *189*, 1620ff.).

Los derivados de hidrazina mono-sustituidos, que se usan en la etapa 1 del esquema 1 se pueden preparar o por desplazamiento nucleófilo en el correspondiente derivado mesilato (esquema 6) o por reducción del intermedio hidrazona como se representa en el esquema 7 [véase, por ejemplo, J.W. Timberlake *et al.*, "*Chemistry of Hydrazo-, Azo-, and Azoxy Groups*"; *Patai,S.,Ed.;* 1975, *Chapter 4*; S. C. Hung *et al.*, *Journal of organic Chemistry 1981*, 46, 5413-5414].

Esquema 6

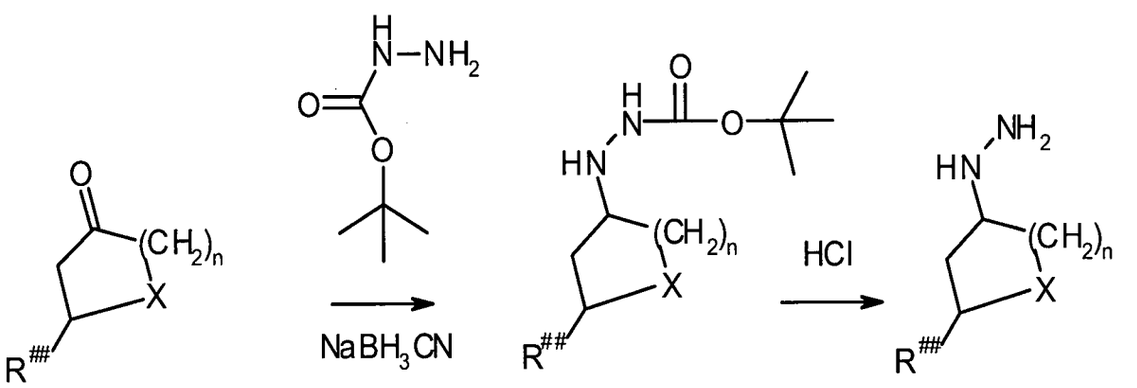


X = O, NH, NR^2, S, SO o SO_2

$R^{##}$ = R^2 o R^3

n = 1,2

Esquema 7



X = O, NH, NR^2, S, SO o SO_2

$R^{##}$ = R^2 o R^3

n = 1,2

Se puede encontrar también información adicional en el documento WO04099210 (en particular en la página 9, último párrafo de la página 14, línea 8, incorporado como referencia).

Los compuestos de la invención presentan una valiosa gama de efectos farmacológicos que podrían no haber sido previstos. Se caracterizan, en particular, por la inhibición de la PDE9A.

Preferiblemente los compuestos según la presente invención presentan un perfil de alta selectividad para la inhibición o modulación de miembros específicos dentro de la familia de las PDE9 u otras familias PDE, con una clara preferencia (selectividad) hacia la inhibición de la PDE9A.

Los compuestos de la presente invención se supone que presentan un perfil de seguridad favorable.

MÉTODO DE TRATAMIENTO

La presente invención se refiere a compuestos que se consideran inhibidores eficaces y selectivos de la fosfodiesterasa 9A y que se pueden utilizar para el desarrollo de medicamentos. Dichos medicamentos se usarán, preferiblemente, para el tratamiento de enfermedades en las que la inhibición de la PDE9A puede generar un efecto terapéutico, profiláctico o modificador de la enfermedad. Preferiblemente, los medicamentos se usarán para mejorar la percepción, concentración, cognición, aprendizaje o memoria, como los que tienen lugar en particular en situaciones/enfermedades/síndromes tales como deterioro cognitivo leve, deterioros del aprendizaje y de la memoria asociados con el envejecimiento, pérdidas de memoria asociadas con el envejecimiento, demencia vascular, traumatismo craneocerebral, ictus, demencia que aparece después de un ictus (demencia post-ictus), demencia post-traumática, deterioros de la concentración general, deterioros de la concentración en niños con problemas de aprendizaje y memoria, enfermedad de Alzheimer, demencia con cuerpos de Lewy, demencia con degeneración de los lóbulos frontales incluyendo el síndrome de Pick, enfermedad de Parkinson, parálisis nuclear progresiva, demencia con degeneración corticobasal, esclerosis lateral amiotrófica (ALS), enfermedad de Huntington, esclerosis múltiple, degeneración talámica, demencia de Creutzfeld-Jacob, demencia por VIH, esquizofrenia con demencia o psicosis de Korsakoff.

Otro aspecto de la presente invención se refiere al tratamiento de una enfermedad que es accesible por modulación de la PDE9A, en particular trastornos del sueño como insomnio o narcolepsia, trastorno bipolar, síndrome metabólico, obesidad, diabetes mellitus incluyendo diabetes tipo 1 o tipo 2, hiperglucemia, dislipidemia, deterioro de la tolerancia a la glucosa o una enfermedad de los testículos, cerebro, intestino delgado, músculo esquelético, corazón, pulmón, timo o bazo.

Por tanto el aspecto médico de la presente invención se puede resumir en que se considera que un compuesto según una cualquiera de las realizaciones prototipo de la invención como se indica aquí, en particular la realización según la fórmula I como se define para cada uno de los aspectos 1 – 17, cada uno de los elementos/realizaciones de la matriz 0 o de la matriz I o un compuesto seleccionado del grupo de los ejemplos de los compuestos finales (véase el aspecto 18 o el capítulo de Realizaciones ilustrativas) se usa como un medicamento.

Dicho medicamento preferiblemente es para el tratamiento de una enfermedad del SNC.

En un uso alternativo, el medicamento es para el tratamiento de una enfermedad del SNC, cuyo tratamiento es accesible mediante la inhibición de la PDE9.

En un uso alternativo, el medicamento es para el tratamiento de una enfermedad que es accesible mediante la inhibición de la PDE9.

En un uso alternativo, el medicamento es para el tratamiento, alivio y / o prevención del deterioro cognitivo que está relacionado con la percepción, concentración, cognición, aprendizaje o memoria.

En un uso alternativo, el medicamento es para el tratamiento, alivio y / o prevención del deterioro cognitivo que está relacionado con los deterioros de aprendizaje y memoria asociados con el envejecimiento, pérdidas de memoria asociadas con el envejecimiento, demencia vascular, traumatismo craneocerebral, ictus, demencia que aparece después de un ictus (demencia post-ictus), demencia post-traumática, deterioros de la concentración general, deterioros de la concentración en niños con problemas de aprendizaje y memoria, enfermedad de Alzheimer, demencia con

cuerpos de Lewy, demencia con degeneración de los lóbulos frontales, incluyendo el síndrome de Pick, enfermedad de Parkinson, parálisis nuclear progresiva, demencia con degeneración corticobasal, esclerosis lateral amiotrófica (ALS), enfermedad de Huntington, esclerosis múltiple, degeneración talámica, demencia de Creutzfeld-Jacob, demencia por VIH, esquizofrenia con demencia o psicosis de Korsakoff.

En un uso alternativo, el medicamento es para el tratamiento de la enfermedad de Alzheimer.

En un uso alternativo, el medicamento es para el tratamiento de trastornos del sueño, trastorno bipolar, síndrome metabólico, obesidad, diabetes mellitus, hiperglucemia, dislipidemia, deterioro de la tolerancia a la glucosa, o una enfermedad de los testículos, cerebro, intestino delgado, músculo esquelético, corazón, pulmón, timo o bazo.

COMPOSICIONES FARMACÉUTICAS

Los medicamentos para administración comprenden un compuesto según la presente invención en una cantidad terapéuticamente eficaz. Por "cantidad terapéuticamente eficaz" se entiende que si el medicamento se aplica mediante el régimen apropiado adaptado a la condición del paciente, la cantidad de dicho compuesto de la fórmula (I) será suficiente para tratar, prevenir o desacelerar de un modo eficaz la progresión de la correspondiente enfermedad, o de otra manera para aliviar el estado de un paciente que padece dicha enfermedad. Puede ocurrir que la "cantidad terapéuticamente eficaz" en una monoterapia difiera de la "cantidad terapéuticamente eficaz" en una terapia combinada con otro medicamento.

El intervalo de dosis de los compuestos de la fórmula general (I) aplicable al día es usualmente de 0,1 a 5000 mg, preferiblemente de 0,1 a 1000 mg, preferiblemente de 2 a 500 mg, más preferiblemente de 5 a 250 mg y lo más preferiblemente de 10 a 100 mg. Una forma farmacéutica unitaria (por ejemplo un comprimido) contiene preferiblemente entre 2 y 250 mg, particularmente preferiblemente entre 10 y 100 mg de los compuestos según la invención.

La cantidad farmacéuticamente eficaz o dosis terapéutica real dependerá naturalmente de factores conocidos por los expertos en la técnica tales como la edad, peso, sexo u otra condición del paciente, la vía de administración, la gravedad de la enfermedad y similares.

Los compuestos según la invención se pueden administrar por vía oral, parenteral (intravenosa, intramuscular etc.), intranasal, sublingual, inhalante, intratecal, tópica o rectal. Las preparaciones adecuadas para administrar los compuestos según la presente invención incluyen por ejemplo, parches, comprimidos, cápsulas, píldoras, pelets, grageas, polvos, comprimidos para chupar, supositorios, preparaciones líquidas tales como soluciones, suspensiones, emulsiones, gotas, jarabes, elixires, o preparaciones gaseosas tales como aerosoles, pulverizaciones y similares. El contenido de los compuestos farmacéuticamente activos debe estar en el intervalo de 0,05 a 90 % en peso, preferiblemente de 0,1 a 50 % en peso de la composición en su totalidad. Se pueden obtener comprimidos adecuados, por ejemplo, mezclando la sustancia o sustancias activas con excipientes conocidos, por ejemplo con diluyentes inertes tales como carbonato de calcio, fosfato de calcio o lactosa, con disgregantes tales como almidón de maíz o ácido algínico, con aglutinantes tales como almidón o gelatina, con lubricantes tales como estearato de magnesio o talco y/o con agentes para retardar la liberación, tales como carboximetilcelulosa, acetato-ftalato de celulosa, o poli(acetato de vinilo). Los comprimidos pueden comprender también varias capas.

Por consiguiente, se pueden preparar comprimidos recubiertos, recubriendo los núcleos producidos de manera análoga a los comprimidos con sustancias normalmente usadas para recubrimientos de comprimidos, por ejemplo, colidona o goma laca, goma arábiga, talco, dióxido de titanio o azúcar. Para conseguir la liberación retardada o evitar incompatibilidades, el núcleo puede consistir también en una serie de capas. Similarmente, el recubrimiento del comprimido puede consistir en una serie de capas para conseguir la liberación retardada, posiblemente usando los excipientes mencionados anteriormente para los comprimidos.

Los jarabes o elixires que contienen las sustancias activas o combinaciones de las mismas de acuerdo con la invención pueden contener adicionalmente un

edulcorante, tal como sacarina, ciclamato, glicerol o azúcar y un potenciador del sabor, p. ej. un saborizante tal como vainillina o extracto de naranja. También pueden contener adyuvantes de suspensión o espesantes tales como carboximetilcelulosa sódica, agentes humectantes tales como, por ejemplo, productos de condensación de alcoholes grasos con óxido de etileno o conservantes tales como p-hidroxibenzoatos.

Las soluciones se preparan de la manera usual, p. ej. con la adición de agentes isotónicos, conservantes, tales como p-hidroxibenzoatos, o estabilizantes, tales como sales de metales alcalinos del ácido etilendiaminotetraacético, usando opcionalmente emulsionantes y/o dispersantes, mientras que si se usa agua como diluyente, por ejemplo, se pueden usar opcionalmente disolventes orgánicos como solubilizantes o adyuvantes de disolución, y las soluciones se pueden transferir a viales o ampollas para inyección o a frascos de perfusión.

Las cápsulas que contienen una o más sustancias activas o combinaciones de sustancias activas se pueden preparar por ejemplo, mezclando las sustancias activas con vehículos inertes tales como lactosa o sorbitol y llenándolas en cápsulas de gelatina.

Se pueden preparar supositorios adecuados, por ejemplo mezclando con vehículos proporcionados para este propósito, tales como grasas neutras o polietilenglicol o los derivados de los mismos.

Los excipientes que se pueden utilizar incluyen, por ejemplo, agua, disolventes orgánicos farmacéuticamente aceptables, tales como parafinas (p. ej. fracciones del petróleo), aceites vegetales (p. ej. aceite de cacahuete o de sésamo), alcoholes mono o polifuncionales (p. ej. etanol o glicerol), vehículos, tales como, p. ej. polvos minerales naturales (p. ej. caolines, arcillas, talco, greda), polvos minerales sintéticos (p. ej. ácido silícico y silicatos altamente dispersados), azúcares (p. ej. azúcar de caña, lactosa y glucosa), emulsionantes (p. ej. lignina, licor de sulfito agotado, metilcelulosa, almidón y polivinilpirrolidona) y lubricantes (p. ej. estearato de magnesio, talco, ácido esteárico y lauril-sulfato de sodio).

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Para uso oral, los comprimidos pueden contener, obviamente, además de los vehículos especificados, aditivos tales como citrato de sodio, carbonato de calcio y fosfato de dicalcio junto con diferentes sustancias adicionales tales como almidón, preferiblemente almidón de patata, gelatina y similares. Para producir los comprimidos también se pueden utilizar lubricantes, tales como estearato de magnesio, lauril-sulfato de sodio y talco. En el caso de suspensiones acuosas, las sustancias activas se pueden combinar con diferentes potenciadores del sabor o colorantes además de los excipientes mencionados anteriormente.

La dosificación de los compuestos según la invención depende, naturalmente, en gran medida del método de administración y de la afección que se esté tratando. Cuando se administran por inhalación, los compuestos de la fórmula (I) se caracterizan por una alta potencia, incluso a dosis en el intervalo de microgramos. Los compuestos de la fórmula (I) se pueden utilizar también eficazmente por encima del intervalo de microgramos. Entonces, la dosificación puede estar en el intervalo de gramos, por ejemplo.

COMBINACIONES CON OTRAS SUSTANCIAS ACTIVAS

En otro aspecto la presente invención se refiere a las formulaciones farmacéuticas mencionadas antes, como tales, que se caracterizan porque contienen un compuesto según la presente invención.

Otro aspecto de la presente invención se refiere a una combinación de cada uno de los compuestos de la presente invención, preferiblemente al menos un compuesto según la presente invención con otro compuesto seleccionado del grupo de, por ejemplo, inhibidores de beta-secretasa; inhibidores de gamma-secretasa; moduladores de gamma-secretasa; inhibidores de la agregación amiloide tal como p. ej., alzhemed; sustancias neuroprotectoras y/o modificadoras de la enfermedad que actúan directa o indirectamente; anti-oxidantes, tales como p. ej., vitamina E, ginko biloba o ginkolide; sustancias antiinflamatorias, tales como p. ej., los inhibidores de la Cox, los NSAID que tienen adicional o exclusivamente propiedades reductoras de Aß; inhibidores de la HMG-CoA reductasa, tales como estatinas; inhibidores de la acetilcolina-esterasa, tales como donepezilo, rivastigmina, tacrina, galantamina; antagonistas del receptor NMDA tales como p. ej., memantina; agonistas del

receptor AMPA; moduladores positivos del receptor AMPA, AMPcinas - inhibidores de la recaptación del receptor de monoamina; sustancias que modulan la concentración o liberación de neurotransmisores; sustancias que inducen la secreción de la hormona del crecimiento tales como ibutamoren-mesilato y capromorelina; antagonistas o agonistas inversos del receptor CB-1; antibióticos tales como minociclina o rifampicina; inhibidores de PDE1, PDE2, PDE4, PDE5 y / o PDE10, agonistas inversos del receptor GABAA; antagonistas del receptor GABAA; agonistas o agonistas parciales del receptor nicotínico; agonistas o agonistas parciales del receptor alfa4beta2-nicotínico; agonistas o agonistas parciales del receptor alfa7-nicotínico; antagonistas de receptor de histamina H3; agonistas o agonistas parciales del receptor 5-HT4; antagonistas del receptor 5-HT6; antagonistas del receptor adrenérgico alfa-2, antagonistas del calcio; agonistas o moduladores positivos del receptor muscarínico M1; antagonistas del receptor muscarínico M2; antagonistas del receptor muscarínico M4; moduladores positivos del receptor 5 de glutamato metabotrópico; antagonistas del receptor 2 de glutamato metabotrópico, y otras sustancias que modulan receptores o enzimas de tal modo que la eficacia y/o seguridad de los compuestos según la invención se aumenta y/o los efectos secundarios no deseados se reducen.

Esta invención se refiere además a composiciones farmacéuticas que contienen una o más sustancias activas, preferiblemente una, que se selecciona de los compuestos según la invención y/o las sales correspondientes, así como una o más sustancias activas, preferiblemente una, seleccionada entre alzhemed, vitamina E, ginkolide, donepezilo, rivastigmina, tacrina, galantamina, memantina, ibutamoren-mesilato, capromorelina, minociclina y/o rifampicina, opcionalmente junto con uno o más vehículos y/o diluyentes inertes.

Los compuestos según la invención se pueden usar también en combinación con inmunoterapias tales como p. ej., inmunización activa con Abeta o partes del mismo o inmunización pasiva con anticuerpos humanizados anti-Abeta o fragmentos de anticuerpos o nanocuerpos para el tratamiento de las enfermedades y trastornos mencionados anteriormente.

Las combinaciones según la presente invención se pueden proporcionar simultáneamente en una y la misma forma farmacéutica, esto es en forma de una preparación de combinación, por ejemplo, se pueden incorporar los dos componentes en un comprimido, p. ej., en diferentes capas de dicho comprimido. La combinación se puede proporcionar también por separado, en forma de una combinación libre, esto es, los compuestos de la presente invención se proporcionan en una forma farmacéutica y uno o más de los compañeros de combinación mencionados antes se proporcionan en otra forma farmacéutica. Estas dos formas farmacéuticas pueden ser las mismas formas farmacéuticas, por ejemplo, una co-administración de dos comprimidos, uno que contiene una cantidad terapéuticamente eficaz del compuesto de la presente invención y uno que contiene una cantidad terapéuticamente eficaz del compañero de combinación mencionado antes. También es posible combinar diferentes formas de administración, si se desea. Se puede proporcionar cualquier tipo adecuado de formas de administración.

El compuesto según la invención, o una de sus sales fisiológicamente aceptables, en combinación con otra sustancia activa se puede usar de forma simultánea o escalonada pero, en particular, dentro de un corto espacio de tiempo. Si se administran de forma simultánea, las dos sustancias activas se administran al paciente juntas; si se administran en tiempos escalonados, las dos sustancias activas se administran al paciente sucesivamente dentro de un periodo de tiempo menor o igual a 12 horas, pero en particular menor o igual a 6 horas.

Las formas farmacéuticas o formas de administración no están limitadas, en el marco de la presente invención se puede usar cualquier forma farmacéutica adecuada. A título de ejemplo, las formas farmacéuticas se pueden seleccionar de preparaciones sólidas tales como parches, comprimidos, cápsulas, píldoras, pelets, grageas, polvos, comprimidos para chupar, supositorios, preparaciones líquidas tales como soluciones, suspensiones, emulsiones, gotas, jarabes, elixires, o preparaciones gaseosas tales como aerosoles, pulverizaciones y similares.

Las formas farmacéuticas se formulan de forma ventajosa en formas farmacéuticas unitarias, siendo adaptada cada forma farmacéutica unitaria para suministrar una única dosis de cada componente activo que está presente. Los ingredientes se

seleccionan en consecuencia dependiendo de la vía de administración y de la forma farmacéutica.

La dosificación para los compañeros de combinación mencionados anteriormente es convenientemente 1/5 de la dosis más baja recomendada normalmente, hasta 1/1 de la dosis recomendada normalmente.

Las formas farmacéuticas se administran al paciente por ejemplo 1, 2, 3, o 4 veces al día dependiendo de la naturaleza de la formulación. En el caso de formulaciones de liberación retardada o prolongada u otras formulaciones farmacéuticas, la administración se puede realizar de forma diferente (p. ej., una vez a la semana o al mes, etc.). Se prefiere que los compuestos de la invención se administren en tres o menos veces, más preferiblemente una o dos veces al día.

EJEMPLOS

COMPOSICIONES FARMACÉUTICAS

Las siguientes formulaciones farmacéuticas pueden ilustrar la presente invención sin limitar su alcance:

A continuación se describen algunos ejemplos de formulaciones en los cuales la expresión "sustancia activa" indica uno o más compuestos según la invención, incluyendo sus sales. En el caso de una de las combinaciones mencionadas antes con una o más de otras sustancias activas, la expresión "sustancia activa" incluye también las sustancias activas adicionales.

Ejemplo A

Comprimidos que contienen 100 mg de sustancia activa

Composición:

1 comprimido contiene:

sustancia activa	100,0 mg

lactosa	80,0 mg
almidón de maíz	34,0 mg
polivinilpirrolidona	4,0 mg
estearato de magnesio	2,0 mg
	220,0 mg

Diámetro: 10 mm, biplano, con facetas en ambos lados y una ranura en un lado.

Ejemplo B

Comprimidos que contienen 150 mg de sustancia activa

Composición:

1 comprimido contiene:

sustancia activa	150,0 mg
lactosa en polvo	89,0 mg
almidón de maíz	40,0 mg
sílice coloidal	10,0 mg
polivinilpirrolidona	10,0 mg
estearato de magnesio	1,0 mg
	300,0 mg

Diámetro: 10 mm, plano

Ejemplo C

Cápsulas de gelatina dura que contienen 150 mg de sustancia activa

1 cápsula contiene:

sustancia activa	150,0 mg
almidón de maíz (desecado)	aprox. 80,0 mg
lactosa (en polvo)	aprox. 87,0 mg
estearato de magnesio	3,0 mg
	aprox. 320,0 mg

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Cubierta de la cápsula: cápsula de gelatina dura de tamaño 1.

Ejemplo D

Supositorios que contienen 150 mg de sustancia activa

1 supositorio contiene:

sustancia activa	150,0 mg
polietilenglicol 1500	550,0 mg
polietilenglicol 6000	460,0 mg
monoestearato de polioxietilen-sorbitán	840,0 mg
	2,000,0 mg

Ejemplo E

Ampollas que contienen 10 mg de sustancia activa

Composición:

sustancia activa		10,0 mg
ácido clorhídrico 0,01 N		c.s.
agua bidestilada	c.s.p.	2,0 mL

Ejemplo F

Ampollas que contienen 50 mg de sustancia activa

Composición:

sustancia activa		50,0 mg
ácido clorhídrico 0,01 N		c.s.
agua bidestilada	c.s.p.	10,0 mL

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La preparación de cualquiera de las formulaciones mencionadas anteriormente se puede efectuar siguiendo procedimientos convencionales.

ENSAYO BIOLÓGICO

Se puede demostrar el efecto *in vitro* de los compuestos de la invención con los siguientes ensayos biológicos.

Protocolo de ensayo de la PDE9A2:

El ensayo de la actividad enzimática de la PDE9A2 se llevó a cabo como un ensayo de centelleo de proximidad (SPA), en general según el protocolo del fabricante (Amersham Biosciences, producto número: TRKQ 7100).

Como fuente enzimática, se usó el lisado (PBS con Triton X-100 al 1 % enriquecido con inhibidores de proteasa, los sedimentos celulares eliminados por centrifugación a 13.000 rpm durante 30 min) de las células SF 9 que expresan la PDE9A2 humana. La cantidad de proteína total incluida en el ensayo varió dependiendo de la infección y eficacia de producción de las células SF9 y oscila entre 0,1 y 100 ng.

En general, las condiciones de ensayo fueron las siguientes:

- volumen de ensayo total: 40 microlitros
- cantidad de proteína: 0,1 – 50 ng
- concentración de sustrato (cGMP): 20 nanomolar; ~1 mCi/l
- tiempo de incubación: 60 min a temperatura ambiente
- concentración final de DMSO: 0,2 - 1 %

Los ensayos se realizaron en un formato de 384 pocillos. Los reactivos de ensayo, así como la enzima y el sustrato, se diluyeron en tampón de ensayo. El tampón de ensayo contenía Tris 50 mM, MgCl2 8,3 mM, EGTA 1,7 mM, BSA al 0,1 %, Tween 20 al 0,05 %; el pH del tampón de ensayo se ajustó a 7,5. Se paró la reacción aplicando un inhibidor específico de la PDE9 (p. ej. los compuestos según el documento WO04099210) en exceso.

Determinación del % de inhibición:

La actividad del control positivo (menos el control negativo = fondo) se fija a 100 % y la actividad en presencia del compuesto de ensayo se expresa con relación a este 100 %. Dentro de este marco, podría ser posible una inhibición por encima del 100 % debido a la naturaleza de la variación del control positivo dentro del ensayo, sin embargo, en este caso el % de inhibición registrado ha sido ajustado al 100 %.

Determinación de la IC_{50}:

La IC_{50} se puede calcular con GraphPadPrism u otro programa informático adecuado, fijando el control positivo como 100 y el control negativo como 0. Para el cálculo de IC_{50}, las diluciones de los compuestos de ensayo (sustratos) se tienen que seleccionar y ensayar siguiendo el protocolo mencionado antes.

Datos

En lo que sigue, los datos de % de inhibición ilustrarán que los compuestos según la presente invención son adecuados para inhibir la PDE9 y por tanto proporcionan propiedades farmacológicas útiles. Los ejemplos no son limitantes. La tabla proporciona también los valores de la IC_{50}. Los valores se presentan dentro de un intervalo nanomolar (nM), esto es, dentro del intervalo de 1 nanomolar a 100 nanomolar o dentro del intervalo de 101 nanomolar a 1200 nanomolar. El valor específico de la IC_{50} está dentro de dicho intervalo. El número del ejemplo se refiere a los ejemplos finales como se indica en la sección **Realizaciones ilustrativas** (véase también el aspecto 18 de la invención).

Todos los datos se miden según el procedimiento descrito aquí.

Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
1	100	1 - 100
2	99	1 - 100
3	99	1 - 100
4	98	1 - 100
5	99	1 - 100
6	98	1 - 100
7	98	1 - 100
8	100	1 - 100
9	99	1 - 100
10	98	1 - 100
11	98	1 - 100
12	97	1 - 100
13	90	101 - 1200
14	96	101 - 1200
15	92	101 - 1200
16	86	101 - 1200
17	100	1 - 100
18	99	1 - 100
19	99	1 - 100
20	98	1 - 100
21	97	101 - 1200
22	98	1 - 100
23	99	1 - 100
24	86	101 - 1200
25	96	1 - 100
26	91	101 - 1200
27	99	1 - 100

Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
28	98	1 - 100
29	96	1 - 100
30	100	1 - 100
31	98	1 - 100
32	100	1 - 100
33	97	1 - 100
34	93	101 - 1200
35	100	101 - 1200
36	100	1 - 100
37	97	1 - 100
38	99	1 - 100
39	99	1 - 100
40	99	1 - 100
40-1	100	1 - 100
40-2	100	1 - 100
40-3	100	101 - 1200
40-4	92	101 - 1200
40-5	98	1 - 100
40-6	97	1 - 100
40-7	95	101 - 1200
41	92	101 - 1200
42	92	101 - 1200
43	98	1 - 100
44	99	1 - 100
45	98	1 - 100
46	100	1 - 100
47	97	1 - 100

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Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
48	96	1 - 100
49	98	1 - 100
50	97	1 - 100
51	96	1 - 100
52	100	1 - 100
53	99	1 - 100
54	97	1 - 100
55	97	1 - 100
56	95	1 - 100
57	100	1 - 100
58	96	1 - 100
60	97	1 - 100
61	97	1 - 100
62	95	1 - 100
63	92	101 - 1200
64	97	1 - 100
65	97	1 - 100
66	91	101 - 1200
67	95	101 - 1200
68	97	1 - 100
69	99	1 - 100
70	99	1 - 100
71	99	1 - 100
72	91	101 - 1200
73	97	1 - 100
74	95	1 - 100
75	98	1 - 100

Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
76	98	1 - 100
77	89	101 - 1200
78	99	101 - 1200
79	99	1 - 100
80	94	1 - 100
81	78	101 - 1200
82	100	1 - 100
83	96	1 - 100
84	97	1 - 100
85	99	1 - 100
86	95	101 - 1200
87	86	101 - 1200
88	96	1 - 100
89	95	101 - 1200
90	100	1 - 100
91	99	1 - 100
92	98	1 - 100
93	97	1 - 100
94	96	101 - 1200
95	98	1 - 100
96	99	1 - 100
97	98	1 - 100
98	97	1 - 100
99	96	1 - 100
100	93	101 - 1200
101	98	1 - 100
102	100	1 - 100

Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
103	99	1 - 100
104	95	101 - 1200
105	84	101 - 1200
106	87	101 - 1200
108	89	101 - 1200
111	88	101 - 1200
112	97	1 - 100
113	92	101 - 1200
114	89	101 - 1200
115	92	101 - 1200
116	93	101 - 1200
117	97	1 - 100
118	89	101 - 1200
119	95	1 - 100
120	95	1 - 100
121	94	101 - 1200
122	85	101 - 1200
123	91	101 - 1200
124	95	101 - 1200
125	95	1 - 100
126	98	1 - 100
127	97	1 - 100
128	99	1 - 100
129	99	1 - 100
130	99	1 - 100
131	97	1 - 100
132	90	101 - 1200

Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
132-1	97	1 - 100
132-2	100	1 - 100
132-3	89	101 - 1200
132-4	98	1 - 100
132-5	100	1 - 100
132-6	99	1 - 100
132-7	94	1 - 100
132-8	94	101 - 1200
132-9	95	101 - 1200
133	98	1 - 100
134	99	1 - 100
135	98	1 - 100
136	100	1 - 100
137	99	1 - 100
138	100	1 - 100
139	99	1 - 100
140	100	1 - 100
141	99	1 - 100
142	98	1 - 100
143	100	1 - 100
144	100	1 - 100
145	84	101 - 1200
146	91	101 - 1200
147	99	1 - 100
147-1	86	101 - 1200
147-2	87	101 - 1200
147-3	95	1 - 100

Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
148	86	101 - 1200
149	95	101 - 1200
150	90	101 - 1200
151	92	101 - 1200
152	93	101 - 1200
153	90	101 - 1200
154	100	1 - 100
155	100	1 – 100
156	99	1 – 100
157	97	1 - 100
158	97	1 - 100
159	100	1 - 100
160	96	1 - 100
161	95	101 - 1200
162	98	1 - 100
163	97	101 - 1200
164	98	101 - 1200
165	99	101 - 1200
166	92	101 - 1200
167	93	101 - 1200
168	90	101 - 1200
169	86	101 - 1200
170	75	101 - 1200
171	100	101 - 1200
172	100	1 - 100
173	86	101 - 1200
174	89	101 - 1200

Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
175	88	101 - 1200
176	85	101 - 1200
177	93	101 - 1200
178	92	101 - 1200
179	91	101 - 1200
180	96	101 - 1200
181	96	1 - 100
182	100	1 - 100
183	99	1 - 100
184	97	1 - 100
185	100	1 - 100
186	97	1 - 100
187	96	1 - 100
188	96	1 - 100
189	90	101 - 1200
190	82	101 - 1200
191	92	101 - 1200
192	100	101 - 1200
193	99	101 - 1200
194	97	101 - 1200
195	88	101 - 1200
196	91	101 - 1200
197	91	101 - 1200
198	100	101 - 1200
199	88	101 - 1200
200	91	101 - 1200
201	85	101 - 1200

Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
202	83	101 - 1200
203	84	101 - 1200
204	87	101 - 1200
205	100	1 - 100
206	82	101 - 1200
207	100	1 - 100
208	100	101 - 1200
209	89	101 - 1200
210	97	1 - 100
211	99	1 - 100
212	92	101 - 1200
213	86	101 - 1200
214	98	1 - 100
215	93	101 - 1200
216	96	1 - 100
217	97	101 - 1200
218	88	101 - 1200
219	100	1 - 100
220	100	1 - 100
221	100	1 - 100

Ejemplo Nº	% inhibición de la PDE9A2 (a concentración 10 micromolar)	IC_{50} dentro del intervalo [nanomolar (nM)]
222	100	1 - 100
223	100	1 - 100
224	100	1 - 100
225	100	1 - 100
226	100	1 - 100
227	100	1 - 100
228	100	1 - 100
229	99	1 - 100
230	100	1 - 100
230-1	98	1 - 100
230-2	100	1 - 100
230-3	99	1 - 100
230-4	98	101 - 1200
231	95	1 - 100
232	99	1 - 100
233	100	1 - 100
234	100	1 - 100
235	98	101 - 1200
236	93	101 - 1200
237	89	101 - 1200

Efecto *in vivo*:

El efecto *in vivo* de los compuestos de esta invención se puede ensayar en el ensayo Novel Object Recognition de acuerdo con el procedimiento de Prickaerts *et al.* (*Neuroscience*, **2002**, *113*, 351-361).

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Para más información sobre ensayos biológicos de los compuestos de la presente invención véase *también Neuropharmacology*, **2008**, *55*, 908-918.

FABRICACIÓN QUÍMICA

Abreviaturas:

APCI	*Ionización química a presión atmosférica*
DAD	*detector por red de diodos*
DMSO	*dimetilsulfóxido*
ESI	*ionización por electronebulización (en MS)*
Ej.	*ejemplo*
Fp.	*punto de fusión*
h	*horas*
HPLC	*cromatografía de líquidos de alta resolución*
HPLC-MS	*cromatografía de líquidos de alta resolución acoplada con detección espectrométrica de masas*
GC-MS	*cromatografía de gases con detección espectrométrica de masas*
MPLC	*cromatografía de líquidos de media presión*
mL	*mililitro*
µL	*microlitro*
min	*minutos*
MS	*espectrometría de masas*
racem.	*racémico*
rt	*temperatura ambiente*
R_t	*tiempo de retención (en HPLC)*
Rf	*factor de retraso (en TLC)*
TBTU	*Tetrafluoroborato de 2-(1 H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio*
TFA	*ácido trifluoroacético*
TLC	*cromatografía en capa fina*

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Métodos LC-MS:

Método A

Instrumento: HPLC/MS ThermoFinnigan. HPLC Surveyor DAD, trampa de iones LCQduo; columna: Sunryse MS-C18, 5 µm, 4,6 x 100 mm; eluyente A: agua + formiato de amonio 20 mM; eluyente B: acetonitrilo + formiato de amonio 20 mM; gradiente: A/B (95:5) durante 1 minuto, después a A/B (5:95) en 7 minutos durante 1,5 minutos; caudal: 0,85 mL/min; detección UV: 254 nm; fuente de iones: ESI

Método 1

Aparato MS tipo: Waters Micromass ZQ; aparato HPLC tipo: Waters Alliance 2695, detector por red de diodos Waters 2996; columna: Varian Microsorb 100 C18, 30 x 4,6 mm, 3,0 µm; eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo; gradiente: 0,0 min 5 % de B → 0,18 min 5 % de B → 2,0 min 98 % de B → 2,2 min 98 % de B → 2,3 min 5 % de B → 2,5 min 5 % de B; caudal: 3,5 mL/min; detección UV: 210-380 nm.

Método 2

Aparato MS tipo: Waters Micromass ZQ; aparato HPLC tipo: Waters Alliance 2695, detector por red de diodos Waters 2996; columna: Merck Chromolith Performance RP18e, 100 x 1 mm; eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo; gradiente: 0,0 min 5 % de B → 0,2 min 5 % de B → 1,6 min 98 % de B → 1,9 min 98 % de B → 2,0 min 5 % de B → 2,2 min 5 % de B; caudal: 3,5 mL/min; detección UV: 210-380 nm.

Método 1D

Instrumento: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; columna: Sunryse MS-C18, 5 µm, 4,6 x 100 mm; eluyente A: 90 % de agua +10 % de acetonitrilo + formiato de amonio 10 mM; eluyente B: acetonitrilo 90 % + 10 % de agua + formiato de amonio 10 mM; gradiente: A (100) durante 1 min, después a B (100) en 7 min durante 1 min; caudal: 1,2 mL/min; detección UV: 254 nm; fuente de iones: APCI.

Método 1E

Instrumento: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; columna: Symmetry C8, 5 µm, 3 x 150 mm; eluyente A: 90 % de agua + 10 % de

acetonitrilo + formiato de amonio 10 mM; eluyente B: acetonitrilo 90 % + 10 % de H_2O + formiato de amonio 10 mM; gradiente: A (100) durante 1,5 min, después a B (100) en 10 min durante 1,5 min; caudal: 1,2 mL/min; detección UV: 254 nm; fuente de iones: APCI

Método 1E fusión

Instrumento: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; columna: Synergi Fusion-RP80A, 4 µm, 4,60 x 100 mm; eluyente A: 90 % de agua + 10 % de acetonitrilo + formiato de amonio 10 mM; eluyente B: acetonitrilo 90 % + 10 % de H_2O + formiato de amonio 10 mM; gradiente: A (100 %) durante 1,5 min, después a B (100 %) en 10 min durante 1,5 min; caudal: 1,2 mL/min; detección UV: 254 nm; fuente de iones: APCI

Método 1E hidro

Instrumento: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; columna: Synergi hydro-RP80A, 4 µm, 4,60 x 100 mm; eluyente A: 90 % de agua + 10 % de acetonitrilo + formiato de amonio 10 mM; eluyente B: acetonitrilo 90 % + 10 % de H_2O + formiato de amonio 10 mM; gradiente: A (100 %) durante 1,5 min, después a B (100 %) en 10 min durante 1,5 min; caudal: 1,2 mL/min; detección UV: 254 nm; fuente de iones: APCI

Método 2F

Instrumento: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, trampa de iones Finnigan LCQduo; columna: Symmetry-C18, 5 µm, 3 x 150 mm; eluyente A: 95 % de agua + 5 % de acetonitrilo + ácido fórmico 0,1 %; eluyente B: acetonitrilo 95 % + 5 % de agua + ácido fórmico 0,1 %; gradiente: A/B (95/5) durante 1,5 min, después a A/B (5/95) en 10 min durante 1,5 min; caudal: 1 mL/min; detección UV: 254 nm; fuente de iones: ESI

Método 2L

Instrumento: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, trampa de iones Finnigan LCQduo; columna: Symmetry Shield, 5 µm, 4,6 x 150 mm; eluyente A: 90 % de agua + 10 % de acetonitrilo + ácido fórmico 0,1 %; eluyente B: acetonitrilo 90

% + 10 % de agua + ácido fórmico 0,1 %; caudal: 0,85 mL/min; detección UV: 254 nm; fuente de iones: ESI

Método Grad_C8_ ácido

Instrumento: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; columna: Xterra MS-C8, 3,5 µm, 4,6 x 50 mm; eluyente A: agua + 0,1 % de TFA + 10 % de acetonitrilo; eluyente B: acetonitrilo; gradiente: A/B (80:20), después a A/B (10:90) en 3,25 minutos durante 0,75 minutos; caudal: 1,3 mL/min; detección UV: 254 nm; fuente de iones: ESI

Método Grad_C18_ ácido

Instrumento: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; columna: Sunfire MS-C18, 3,5 µm, 4,6 x 50 mm; eluyente A: agua + 0,1 % de TFA + 10 % de acetonitrilo; eluyente B: acetonitrilo; gradiente: A/B (80:20), después a A/B (10:90) en 3,25 minutos durante 0,75 minutos; caudal: 1,3 mL/min; detección UV: 254 nm; fuente de iones: ESI.

Método Grad_90_10_C8_ácido

Instrumento: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; columna: Xterra MS-C8, 3,5 µm, 4,6 x 50 mm; eluyente A: agua + 0,1 % de TFA + 10 % de acetonitrilo; eluyente B: acetonitrilo; gradiente: A (100 %), después a A/B (10:90) en 3,25 min durante 0,75 min; caudal: 1,3 mL/min; detección UV: 254 nm; fuente de iones: ESI.

Método Grad_90_10_C18_ácido

Instrumento: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; columna: Xterra MS-C18, 3,5 µm, 4,6 x 50 mm; eluyente A: agua + 0,1 % de TFA + 10 % de acetonitrilo; eluyente B: acetonitrilo; gradiente: A (100), después a A/B (10:90) en 3,25 min durante 0,75 min; caudal: 1,3 mL/min; detección UV: 254 nm; fuente de iones: ESI.

Método Grad_C8_NH4COOH

Instrumento: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole. Columna: Xterra MS-C8, 3,5 µm, 4,6 x 50 mm; eluyente A: agua + formiato de

amonio 5 mM + 10 % de acetonitrilo; eluyente B: acetonitrilo; gradiente: A 100 %, después a A/B (10:90) en 3,25 min durante 0,75 min; caudal: 1,3 mL/min; detección UV: 254 nm; fuente de iones: ESI.

Métodos de HPLC quiral

Instrumento: Agilent 1100. Columna: Chiralpak AS-H Daicel, 4,6 µm, 4,6 x 250 mm;

Método quiral 1: eluyente: hexano/etanol 97/3 (isocrático); caudal: 1,0 mL/min; detección UV: 254 nm.

Método quiral 2: eluyente: hexano/etanol 98/2 (isocrático); caudal: 1,0 mL/min; detección UV: 254 nm

Método quiral 3: eluyente: hexano/etanol 80/20 (isocrático); caudal: 1,0 mL/min; detección UV: 254 nm

Métodos de GC/MS

Método 3A

Instrumento: GC/MS Finnigan. Trace GC, MSQ quadrupole. Columna: DB-5MS, 25 m x 0,25 mm x 0,25 µm; gas portador: helio, caudal constante de 1 mL/min; programa de la estufa: 50 °C (mantener 1 minuto), eluyente a 100 °C en 10°C/min, a 200 °C en 20°C/min, a 300 °C en 30°C/min, detección: trace MSQ, quadrupole fuente de iones: IE intervalo de barrido: 50-450 u.

Método 3A.1

Instrumento: GC/MS Finnigan Thermo Scientific. Trace GC Ultra, DSQ II single quadrupole. Columna: DB-5MS UI, 25 m x 0,25 mm x 0,25 µm; gas portador: helio, caudal constante de 1 mL/min; programa de la estufa: 50 °C (mantener 1 minuto), eluyente a 100 °C en 10°C/min, a 200 °C en 20°C/min, a 300 °C en 30°C/min, detección: trace DSQ, single quadrupole

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Calentamiento en microondas:

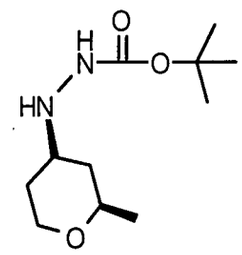
Tipos de aparatos de microondas:

- Instrumentos Discover® CEM, equipados con recipientes de 10 y 35 mL;
- Aparato de microondas tipo: Biotage Initiator Sixty.

Comentario general en relación con la presentación de las estructuras

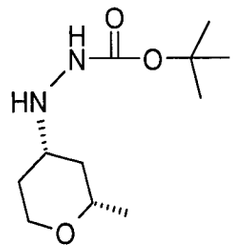
Algunos compuestos tienen uno o más centros quirales. La estructura representada no mostrará necesariamente todas las posibles realizaciones estereoquímicas del compuesto sino solamente una. Sin embargo, en tales casos se añade un término como "mezcla cis-racémica" cerca de la estructura con el fin de señalar las otras opciones estereoquímicas.

Se da un ejemplo en el Ejemplo 7D, que sigue. La fórmula estructural presentada es



Mezcla cis-racémica

El término añadido "mezcla cis-racémica" indica una segunda opción estereoquímica:



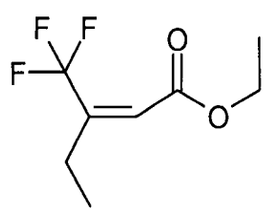
Este principio se aplica también a otras estructuras representadas.

Síntesis

A continuación se describe la fabricación de compuestos como ejemplos de la presente invención. En el caso en que el procedimiento de fabricación de un compuesto específico no haya sido descrito literalmente, las personas expertas en la técnica encontrarán una descripción de procedimientos análogos dentro de estas descripciones que pueden seguir en principio. En algunos sitios se dice, que los ejemplos se pueden preparar de manera análoga a otro ejemplo. Si se hace referencia a dicho "procedimiento análogo" las condiciones de reacción son aproximadamente las mismas, aún cuando las relaciones molares de reactivos y eductos pueden ser ajustadas. También será evidente que los materiales de partida dentro de un procedimiento descrito se pueden variar químicamente para conseguir los mismos resultados, esto es, si se describe la reacción de condensación de un éster, en la que el componente alcohólico es un grupo saliente pero no objeto del producto, este componente alcohólico puede variar sin cambios significativos del procedimiento como tal.

Compuestos de partida:

Ejemplo 1A

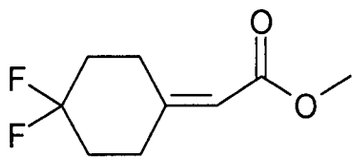


Se enfrió a 0 °C una solución de 70 g (201 mmol) de carbetoximetilen-trifenilfosforano en 300 mL de éter dietílico y se añadieron 25 g (198 mmol) de 1,1,1-trifluorobutanona. Se calentó la solución a temperatura ambiente y se agitó durante la noche. Se filtró la mezcla de reacción y se concentró el filtrado a presión reducida (700 mbar y temperatura del baño 40 °C). Se purificó el residuo por destilación a vacío (170 mbar y temperatura del baño 130 °C, fracción principal: 95-96 °C). Se obtuvieron 29 g (75 %) del producto como un aceite incoloro.

HPLC-MS (Método 1): tiempo de retención: 1,77 min

MS (ESI pos): m/z = 196 (M+H)+

Ejemplo 1AA



Se suspendieron 400 mg (10,0 mmol) de hidruro de sodio (al 60 % en aceite mineral) en 10 mL de THF y se enfriaron a 4 °C. Mientras se agitaba, se añadió una solución de 1,3 mL (8,99 mmol) de acetato de trimetilfosfono en 10 mL de THF. Se agitó la mezcla durante 1 h a la misma temperatura. Después de esto, se añadió una solución de 4,4-difluorociclohexanona en 10 mL de THF a 0 °C. Se dejó que se calentara la mezcla a temperatura ambiente y se agitó durante 14 h. Se añadieron THF y agua y se evaporó el THF. Se diluyó el resto con acetato de etilo, se lavó con agua y solución saturada de hidrogenocarbonato de sodio y se evaporó para dar 1,49 g (95 %) del producto.

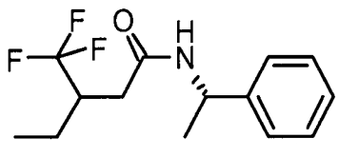
MS (EI): m/z = 190 $(M)^+$

Los siguientes ejemplos 1B, 1C, 1D, 1E, 2A, 2B, 2C y 2D muestran cómo los ácidos racémicos ácido 3-trifluorometil-pentanoico y ácido 3-trifluorometil-butírico pueden

ser cambiados a las dos formas enantiómeras del ácido libre. La resolución se puede llevar a cabo mediante la separación de intermedios diastereoisómeros. Las dos formas enantiómeras puras del ácido libre se denominarán enantiómero A y enantiómero B respectivamente. Los correspondientes intermedios diastereoisómeros se denominarán diastereoisómero A y diastereoisómero B respectivamente.

Se puede aplicar el mismo principio para la resolución enantiómera de otras mezclas racémicas si fuera apropiado.

Ejemplo 1B



Diastereoisómero A

Se agitó una solución de ácido 3-trifluorometil-pentanoico racémico (8 g, 47 mmol), TBTU (16,6 g, 52 mmol) y diisopropiletilamina (24,1 mL, 141 mmol) en dimetilformamida (80 mL) a 20 °C durante 1 h, después se añadió (*S*)-(−)-1-feniletilamina (10 g, 82 mmol) y se agitó la mezcla durante 16 h a 20 °C. Se separó el disolvente y se añadió diclorometano (200 mL). Se lavó la mezcla resultante con ácido cítrico al 10 % en agua (200 mL), $K2CO_3$ al 20 % en agua (100 mL) y se secó sobre sulfato de sodio. Por evaporación del disolvente se obtuvo un sólido crudo que se mezcló con metanol (10 mL) y se filtró a través de un lecho de alúmina básica activada. La separación de los diastereoisómeros se obtuvo por cromatografía rápida sobre SiO_2 eluyendo con una mezcla de ciclohexano/acetato de etilo 85/15.

Se obtuvieron 4,5 g (35,8 %) del compuesto del epígrafe como un sólido blanco.

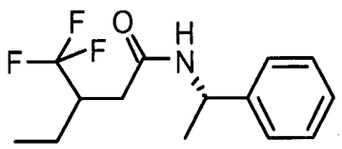
Rf: 0,25 (ciclohexano/acetato de etilo 85/15, teñido con $KMnO_4$ básico)

HPLC-MS (Método 1E hidro): tiempo de retención: 9,35 min

MS (APCI pos): m/z = 274 $(M+H)^+$.

HPLC quiral (Método quiral 1): tiempo de retención: 5,58 min de: >99 %

Ejemplo 1C



Diastereoisómero B

Se obtuvieron 4,4 g (34,2 %) de un sólido blanco como segundo producto a partir de la cromatografía rápida del Ejemplo 1B.

Rf: 0,20 (ciclohexano/acetato de etilo 85/15, teñido con $KMnO_4$ básico)

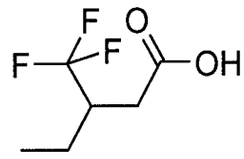
HPLC-MS (Método 1E hidro): tiempo de retención: 9,33 min

MS (APCI pos): m/z = 274 $(M+H)^+$.

HPLC quiral (Método quiral 1): tiempo de retención: 6,18 min de: >99 %

Ejemplo 1D

Ácido 3-trifluorometil-pentanoico, Enantiómero A



Enantiómero A

Una solución del Ejemplo 1B (4,6 g, 17 mmol) en dioxano (15 mL) se trató con H_2SO_4 al 70 % en agua (25 mL) y se mantuvo a reflujo durante 16 h. Se enfrió la mezcla, se alcalinizó hasta pH 14 con NaOH al 32 % en agua, se diluyó con agua (50 mL) y se extrajo con diclorometano (2x 200 mL). Se acidificó la solución resultante hasta pH 1 con HCl 9 N, se extrajo con diclorometano (3x 500 mL) y las fases orgánicas reunidas se secaron. Por evaporación del disolvente se obtuvieron 2,47 g (86,3 %) de un aceite pardo.

Rf: 0,66 (diclorometano/metanol 9/1, teñido con verde de bromocresol)

HPLC quiral (Método quiral 1): tiempo de retención 5,58 min ee: >99 %

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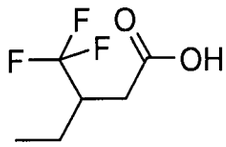
Ejemplo 1E

Ácido 3-trifluorometil-pentanoico, Enantiómero B



Enantiómero B

Análogamente a la preparación del Ejemplo 1D, se obtuvo el compuesto del epígrafe utilizando el Ejemplo 1C como material de partida.

Rendimiento: 80,3 %

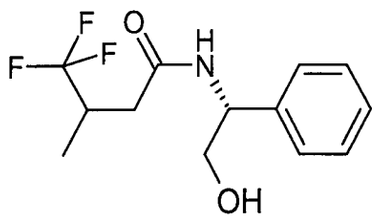
Rf: 0,66 (diclorometano/metanol 9/1, teñido con verde de bromocresol)

HPLC quiral (Método quiral 1): tiempo de retención: 5,08 min ee: >99 %

Ejemplo 2A

4,4,4-Trifluoro-N-((R)-2-hidroxi-1-fenil-etil)-3-metil-butiramida,

Diastereoisómero A



Una solución de ácido 3-(trifluorometil)butírico (10 g, 64 mmol) en dimetilformamida (100 mL) se trató con hidrocloruro de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (14,7 g, 77 mmol), 4-dimetil-amino-piridina (11 g, 89,7 mmol) y (R)-(-)-fenilglicinol (9,9 g, 70,5 mmol). Se agitó la mezcla a 20 °C durante 16 h, después se concentró para reducir el volumen y se trató con ácido cítrico al 10 % en agua (300 mL). Se extrajo la mezcla con éter etílico (2 x 200 mL) y las fases orgánicas separadas se lavaron con NaHCO3 al 10 % (150 mL) y salmuera (150 mL). Se secó la fase orgánica y se evaporó para dar 13,1 g de un sólido blanco crudo.

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La separación de los diastereoisómeros se realizó por cromatografía rápida sobre SiO_2 eluyendo con una mezcla de acetato de etilo/hexano 6/4.

Se obtuvieron 5,32 g (30,2 %) del compuesto del epígrafe como un sólido blanco.

Rf: 0,23 (acetato de etilo/hexano 6/4)

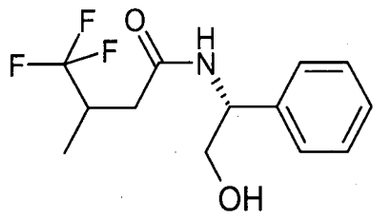
HPLC-MS (1E hidro): tiempo de retención: 6,97 min

MS (APCI pos): m/z = 276 $(M+H)^+$.

Ejemplo 2B

4,4,4-Trifluoro-N-((R)-2-hidroxi-1-fenil-etil)-3-metil-butiramida,

Diastereoisómero B



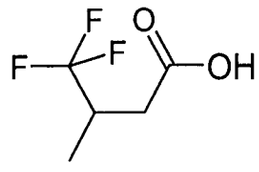
Se obtuvieron 3,08 g (17,5 %) de un sólido blanco como segundo producto a partir de la cromatografía rápida del Ejemplo 2A.

Rf: 0,16 (acetato de etilo/hexano 6/4)

HPLC-MS (1E hidro): tiempo de retención: 6,92 min

MS (APCI pos): m/z = 276 $(M+H)^+$.

Ejemplo 2C, Enantiómero A



Una solución del Ejemplo 2A (2 g, 7,26 mmol) en tetrahidrofurano (10 mL) se trató con H_2SO_4 al 70 % en agua (10 mL) y se mantuvo a reflujo durante 16 h. Se enfrió la mezcla, se alcalinizó hasta pH 14 con NaOH al 32 % en agua, se diluyó con agua (50 mL) y se extrajo con diclorometano (2x 50 mL). Se acidificó la solución resultante hasta pH 1 con HCl 9 N, se extrajo con diclorometano (3x 50 mL) y las fases

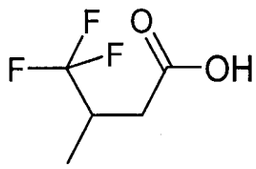
orgánicas reunidas se secaron. Por evaporación del disolvente se obtuvieron 0,84 g (74,1 %) de un aceite pardo.

HPLC-MS (1E hidro): tiempo de retención: 1,73 min

MS (APCI neg): m/z = 155 (M-H)-.

HPLC quiral (Método quiral 2): tiempo de retención: 6,92 min ee: 99 %

Ejemplo 2D, Enantiómero B



Análogamente a la preparación del Ejemplo 2C, se obtuvo el compuesto del epígrafe utilizando el Ejemplo 2B como material de partida. Se obtuvieron 1,4 g (8,96 mmol)

Rendimiento: 82,3 %

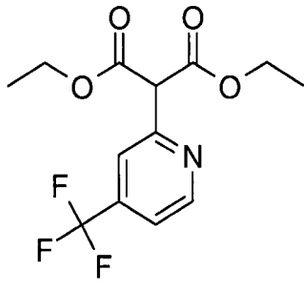
HPLC-MS (1E hidro): tiempo de retención: 1,30 min

MS (APCI neg): m/z = 155 (M-H)-.

HPLC quiral (Método quiral 2): tiempo de retención: 6,49 min ee: 98,6 %

Ejemplo 3A

Éster dietílico del ácido 2-(4-trifluorometil-piridin-2-il)-malónico



Una suspensión de hidruro de sodio al 60 % en aceite mineral (1,65 g, 41 mmol) en dioxano anhidro (36 mL) se trató con malonato de dietilo (6,3 mL, 41 mmol) a 25 °C y se calentó a 60 °C durante 30 min. Se añadió cloruro cuproso (1,63 g, 17 mmol), se calentó la mezcla a 80 °C y se añadió 2-cloro-4-(trifluorometil)-piridina y se aumentó el calentamiento a 100 °C durante 16 h.

Después de enfriar a 20 °C se acidificó la mezcla con HCl al 37 %, se diluyó con agua (120 mL) y se extrajo con diclorometano (2 x 60 mL). Se secó la fase orgánica y se evaporó para dar un aceite crudo que se purificó por cromatografía rápida eluyendo con *n*-hexano/acetato de etilo de 95/5 a 60/40.

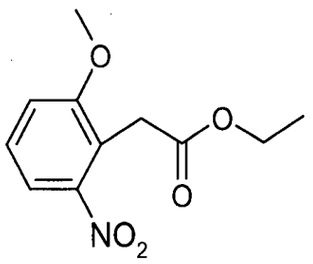
Se obtuvieron 1,9 g (38 %) como un aceite incoloro.

HPLC-MS (2F): tiempo de retención: 12,24 min

MS (ESI pos): m/z = 306 $(M+H)^+$.

Ejemplo 4A

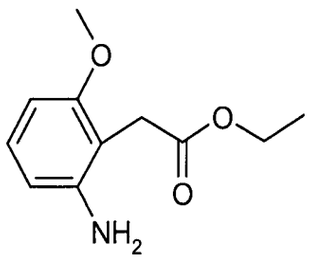
El siguiente ejemplo se sintetizó de manera análoga a la preparación del Ejemplo 5U, utilizando el correspondiente ácido (Sinova Inc., Bethesda, MD 20814, USA) como material de partida.



HPLC-MS (Método 1): tiempo de retención: 1,47 min

MS (ESI pos): m/z = 194 $(M+H-EtOH)^+$

Ejemplo 4B



Se disolvieron 2,0 g (8,6 mmol) del Ejemplo 4A en 40 mL de etanol, se añadió Pd (al 10 % sobre carbón), y se hidrogenó la mezcla a temperatura ambiente (2 h, 344,8

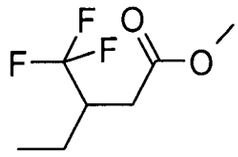
kPa). Se filtró la mezcla de reacción y se lavó el residuo con etanol. Se evaporó el disolvente a presión reducida. Se obtuvieron 1,80 g (100 %) del producto.

HPLC-MS (Método 1): tiempo de retención: 0,91 min

MS (ESI pos): m/z = 210 $(M+H)^+$

Ejemplo 5A

Éster metílico del ácido 3-trifluorometil-pentanoico, Enantiómero A



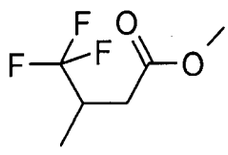
Enantiómero A

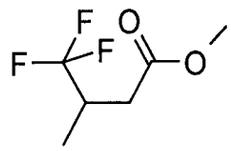
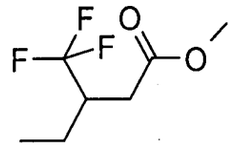
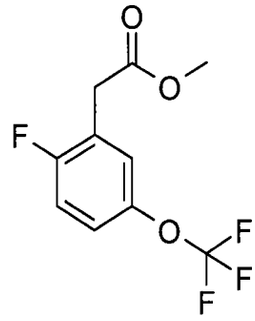
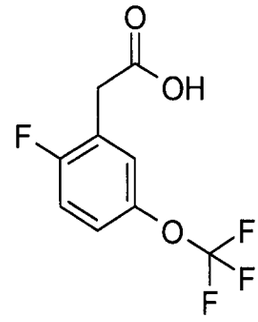
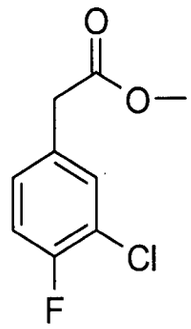
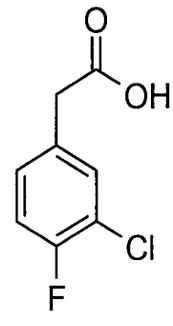
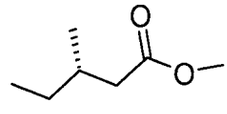
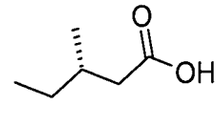
A una solución en agitación del Ejemplo 1D (250 mg, 1,47 mmol) en diclorometano (10 mL) y metanol (0,25 mL), en atmósfera de nitrógeno, se añadió trimetilsilildiazometano (solución 2,0 M en éter dietílico) (2,1 mL, 4,19 mmol) gota a gota a 0 °C. Se agitó la mezcla de reacción manteniendo la temperatura por debajo de 5 °C durante 1 h. Se separó el disolvente (40 °C, 25 bar) dando 250 mg (75,4 %) de un aceite amarillo que se utilizó en la siguiente etapa sin purificación adicional.

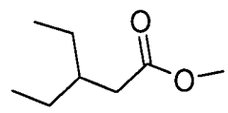
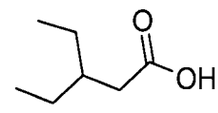
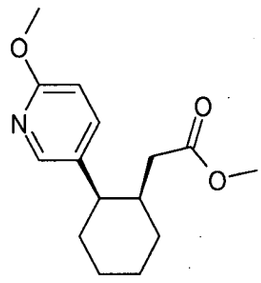
GC (Método 3A): tiempo de retención: 3,29 min

MS (EI): m/z: 165 $(M-19)^+$,155 $(M-29)^+$, 153 $(M-31)^+$

Los siguientes ejemplos fueron sintetizados análogamente a la preparación del Ejemplo 5A, utilizando los correspondientes ácidos como materiales de partida:

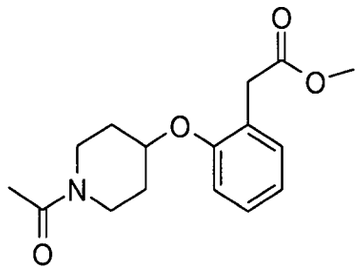
	estructura	material de partida: ácido carboxílico	tiempo de retención [min]	MS *m/z*
Ejemplo 5B Enantió-		Ejemplo 2C	8,01 (Método 3A)	170 [EI]

	estructura	material de partida: ácido carboxílico	tiempo de retención [min]	MS *m/z*
mero A				
Ejemplo 5C Enantió-mero B		Ejemplo 2D	8,01 (Método 3A)	170 [EI]
Ejemplo 5D Enantió-mero B		Ejemplo 1E	3,29 (Método 3A)	165(M-19)$^+$, 155(M-29)$^+$, 153(M-31)$^+$ [EI]
Ejemplo 5E			7,82 (Método 3A)	252 [EI]
Ejemplo 5F			9,53 (Método 3A)	202 [EI]
Ejemplo 5G Enantió-mero S			3,92 (Método 3A)	130 [EI]

	estructura	material de partida: ácido carboxílico	tiempo de retención [min]	MS *m/z*
Ejemplo 5H			5,09 Método 3A	115 $(M-29)^{\pm}$ [EI]
Ejemplo 5HA mezcla cis, racémica		Ejemplo 18A	1,22 (Método 1)	264 [ESI, $(M+H)^+$]

Ejemplo 5I

Éster metílico del ácido [2-(1-acetil-piperidin-4-iloxi)-fenil]-acético

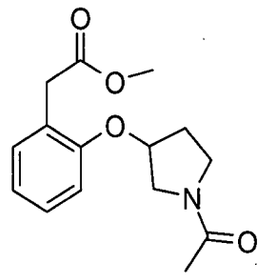
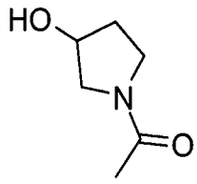
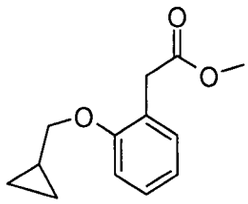
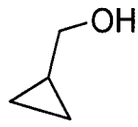
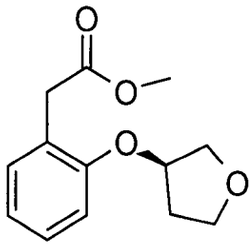
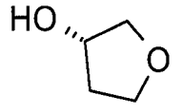
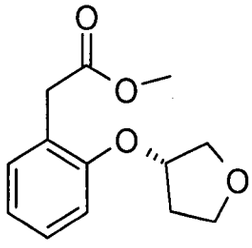
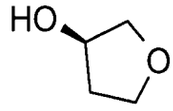


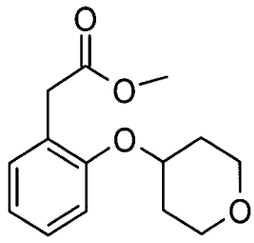
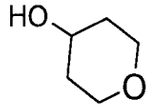
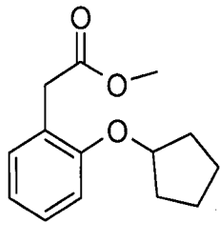
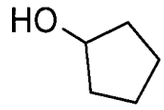
Se vertió azodicarboxilato de di-*terc*-butilo (305 mg, 1,32 mmol) a una solución de 1-(4-hidroxi-piperidin-1-il)-etanona (259 mg, 1,8 mmol) en tetrahidrofurano (4 mL) en atmósfera de nitrógeno. Se añadieron después éster metílico del ácido (2-hidroxi-fenil)-acético (200 mg, 1,2 mmol) y trifenilfosfina (347 mg, 1,3 mmol). Se agitó la mezcla amarilla a 20 °C durante 16 h. Se evaporó el disolvente y se purificó el residuo sobre sílice utilizando mezcla de hexano/acetato de etilo de polaridad creciente (de 70 % a 100 % de acetato de etilo) como eluyente para dar 195 mg (55,6 %) de un aceite incoloro.

HPLC-MS (Método Grad_C8_NH_4COOH): tiempo de retención: 2,67 min

MS (ESI pos): m/z = 292 $(M+H)^+$.

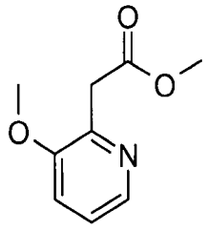
Los siguientes ejemplos fueron sintetizados análogamente a la preparación del Ejemplo 5G, utilizando los correspondientes alcoholes como materiales de partida:

	Estructura	material de partida: Alcohol	Rf	tiempo de retención [min]	MS m/z
Ejemplo 5J mezcla racémica				2,53 (Método Grad_C8_ NH_4COOH)	292 $(M+H)^+$
Ejemplo 5K			0,35 (hexano/ acetato de etilo 8/2)		
Ejemplo 5L			0,2 (hexano/ acetato de etilo 7/3)		
Ejemplo 5M			0,2 (hexano/ acetato de etilo 7/3)		

	Estructura	material de partida: Alcohol	Rf	tiempo de retención [min]	MS m/z
Ejemplo 5O			0,25 (hexano/ acetato de etilo 7/3)		
Ejemplo 5P			0,35 (hexano/ acetato de etilo)		

Ejemplo 5Q

Éster metílico del ácido (3-metoxi-piridin-2-il)-acético



Una mezcla de (3-metoxi-2-piridin-2-il)-acetonitrilo (400 mg, 2,7 mmol) en 2 mL de metanol y ácido sulfúrico al 96 % (1,8 mL, 32 mmol), se calentó en un horno de microondas a 120 °C durante 1 h. Se enfrió la mezcla a 0 °C, se alcalinizó con $NaHCO_3$ sólido, se diluyó con agua (2 mL) y se extrajo con diclorometano. La fase orgánica separada se secó y se evaporó para dar 450 mg (92 %) de un aceite amarillo oscuro que se usó en la siguiente etapa sin purificación adicional.

HPLC-MS (Método Grad_C8_NH_4COOH): tiempo de retención: 1,92 min

MS (ESI pos): m/z = 182 $(M+H)^+$.

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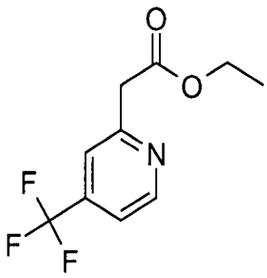
Ejemplo 5R

Éster etílico del ácido (4-trifluorometil-piridin-2-il)-acético



Una solución del Ejemplo 3A (1,0 g, 3,27 mmol) en DMSO anhidro (8 mL) se trató con agua (60 microL, 3,27 mmol) y cloruro de litio (347 mg, 8,2 mmol). Se calentó la mezcla resultante a 120 °C durante 16 h. Después de enfriar a 20 °C se trató la mezcla con salmuera (12 mL) y se extrajo con acetato de etilo (3 x 20 mL). Se secó la fase orgánica y se evaporó para dar un aceite crudo que se purificó por cromatografía rápida eluyendo con *n*-hexano/acetato de etilo 8/2.

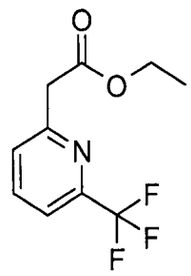
Se obtuvieron 390 mg (51 %) como un aceite incoloro.

HPLC-MS (Método 2F): tiempo de retención: 11,09 min

MS (ESI pos): m/z = 234 $(M+H)^+$

Ejemplo 5S

Éster etílico del ácido (6-trifluorometil-piridin-2-il)-acético



Una mezcla de carbonato de cesio (1,87 g, 5,75 mmol) y tri-t-butilfosfina (107 µL, 0,44 mmol) en 1,2 dimetoxietano seco (10 mL) se trató con tris-(dibencilidenacetona)di-paladio (81 mg, 0,09 mmol), 2-bromo-6-(trifluorometil)piridina (1 g, 4,42 mmol) y malonato de dietilo (0,8 mL, 5,3 mmol) en atmósfera de nitrógeno. Se calentó la mezcla a 150 °C durante 30 min en un horno de microondas. Después de enfriar a 20 °C se trató la mezcla con una solución saturada de cloruro de amonio

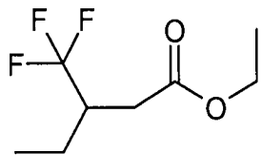
(120 mL) y se extrajo con éter etílico (3 x 80 mL). Se secó la fase orgánica y se evaporó para dar un aceite crudo que se purificó por cromatografía rápida eluyendo con *n*-hexano/éter etílico 6/1.

Se obtuvieron 460 mg (81 %) como un aceite incoloro.

GC (Método 3A): tiempo de retención: 8,28 min

MS (EI): m/z = 233 $(M)^+$

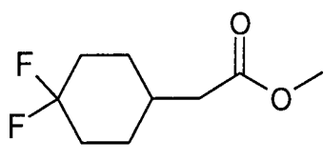
Ejemplo 5T, mezcla racémica



Se reunieron 29 g (148 mmol) del Ejemplo 1A con 2 g de Pd/C (al 10 %) y se hidrogenaron a temperatura ambiente (6 h, 103,4 kPa). Se filtró la mezcla de reacción y se lavó con éter dietílico. Se evaporó el disolvente a presión reducida (500 mbar, temperatura del baño 40 °C). Se obtuvieron 27,6 g (94 %) del producto como un líquido incoloro.

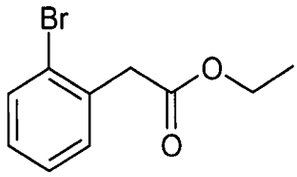
HPLC-MS (Método 1): tiempo de retención: 1,65 min

Ejemplo 5TA



Se disolvieron 1,49 g (95 %, 7,43 mmol) en 20 mL de etanol y se hidrogenaron sobre 150 mg de Pd/C (al 10 %) a presión atmosférica durante 14 h. Se filtró la mezcla y se separó el disolvente para dar 1,27 g (89 %) del producto.

Ejemplo 5U

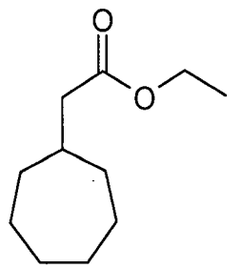
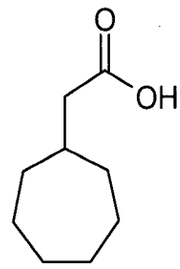
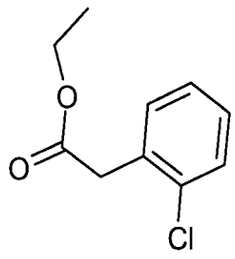
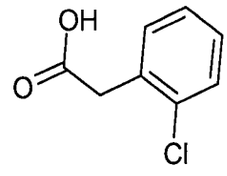
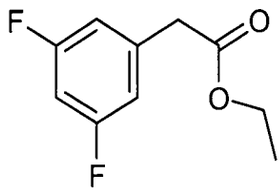
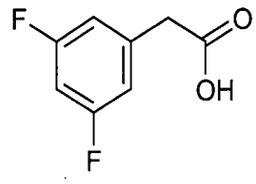
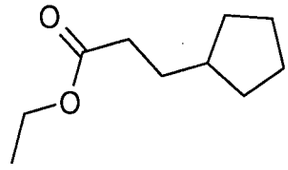
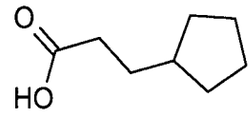
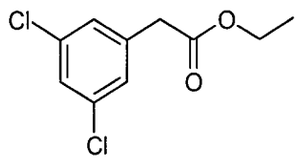
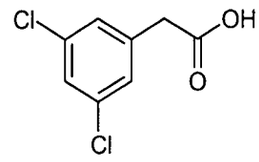
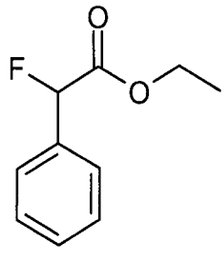
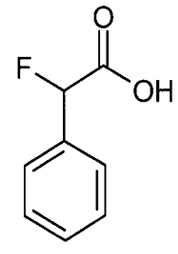


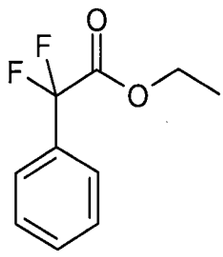
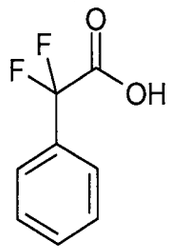
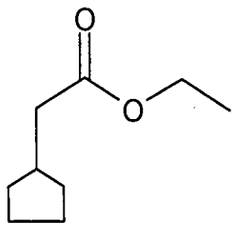
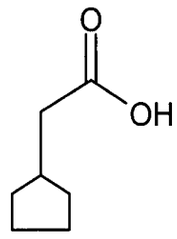
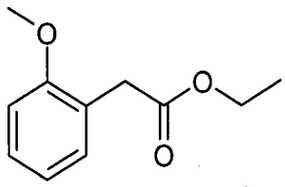
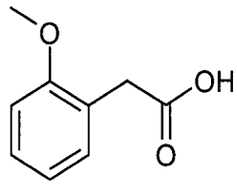
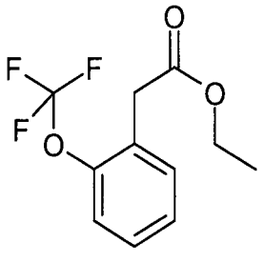
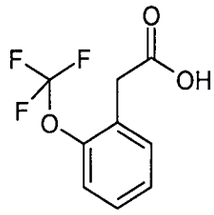
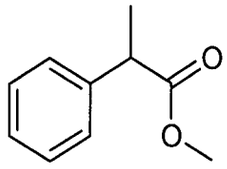
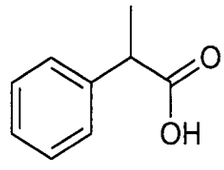
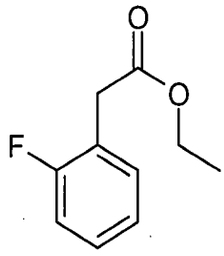
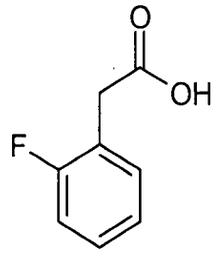
Una solución de 15 g (69,8 mmol) de ácido (2-bromo-fenil)-acético en 50 mL de etanol se enfrió a 0 °C y se añadieron gota a gota 8 mL (110 mmol) de cloruro de tionilo. Se calentó la mezcla de reacción a 50 °C durante la noche. Después de enfriar a temperatura ambiente se separó el disolvente a presión reducida. Se mezcló el residuo con acetato de etilo y se filtró sobre 30 g de óxido de aluminio básico. Se evaporó el filtrado a presión reducida. Se obtuvieron 18 g (92 %) del producto.

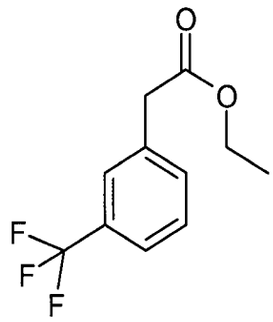
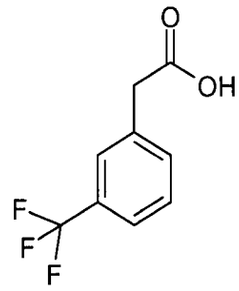
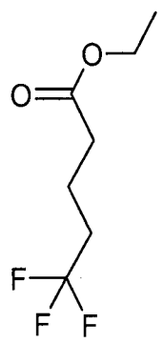
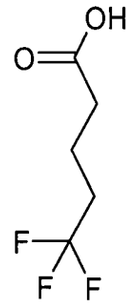
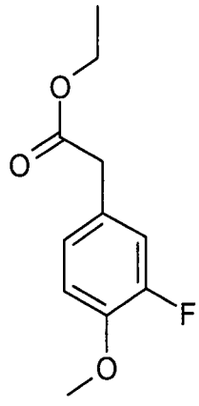
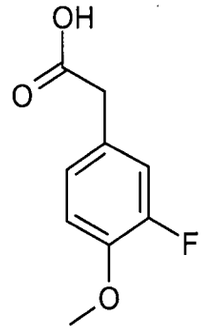
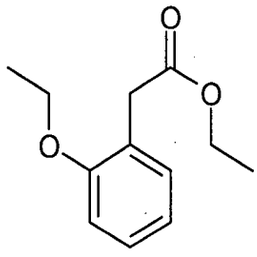
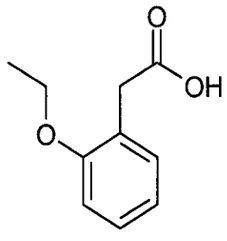
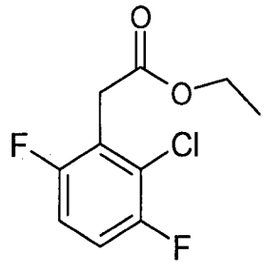
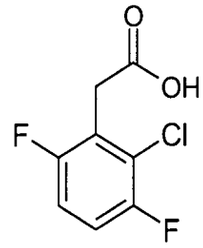
HPLC-MS (Método 1): tiempo de retención: 1,62 min

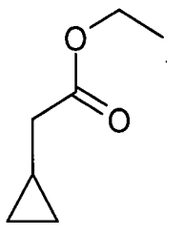
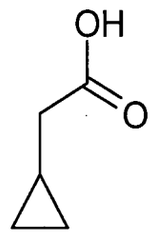
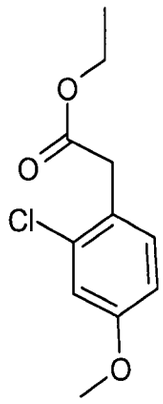
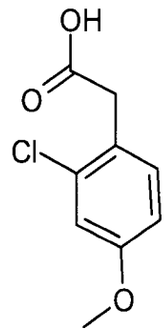
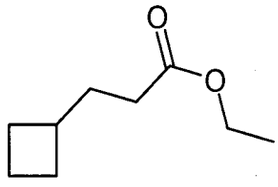
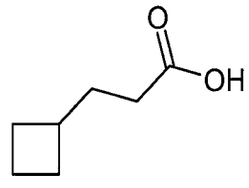
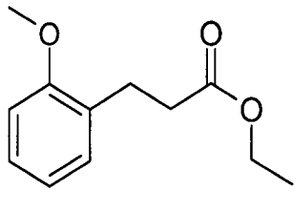
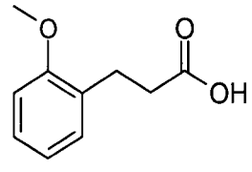
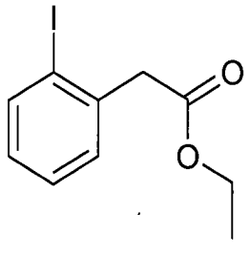
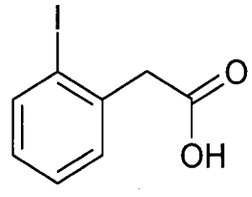
MS (ESI pos): m/z = 243/45 (Br) $(M+H)^+$

Los siguientes ejemplos fueron sintetizados análogamente a la preparación del Ejemplo 5U, utilizando los correspondientes ácidos como materiales de partida.

	estructura	material de partida	tiempo de retención [min]	MS (ESI m/z)
Ej. 5V				185 $(M+H)^+$
Ej. 5Y			1,56 (Método 1)	199/201 (Cl) $(M+H)^+$
Ej. 5W			1,53 (Método 1)	201 $(M+H)^+$
Ej. 5X				171 $(M+H)^+$
Ej. 5Z			1,74 (Método 1)	233/235/237 (2Cl) $(M+H)^+$
Ej. 5AA mezcla racémica				133 $(M+H)^+$

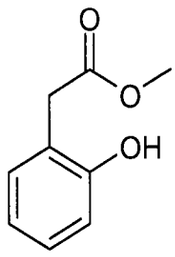
Ej. 5AB				201 $(M+H)^+$
Ej. 5AC			1,65 (Método 1)	157/58 $(M+H)^+$
Ej. 5AD			1,36 (Método 1)	195 $(M+H)^+$
Ej. 5AE			1,69 (Método 1)	249/50 $(M+H)^+$
Ej. 5AF mezcla racémica				Comercial-mente disponible
Ej. 5AG			1,46 (Método 1)	

Ej. 5AH			1,63 (Método 1)	
Ej. 5AI				185 $(M+H)^+$
Ej. 5AJ			1,43 (Método 1)	213 $(M+H)^+$
Ej. 5AK				
Ej. 5AL			1,58 (Método 1)	235/237 (Cl) $(M+H)^+$

Ej. 5ALA			1,29 (Método 1)	129 $(M+H)^+$
Ej. 5ALB			1,54 (Método 1)	229/231 (Cl) $(M+H)^+$
Ej. 5ALC			1,62 (Método 1)	157 $(M+H)^+$
Ej. 5ALD			1,56 (Método 1)	209 $(M+H)^+$
Ej. 5ALE			1,59 (Método 1)	291 $(M+H)^+$

Ejemplo 5AM

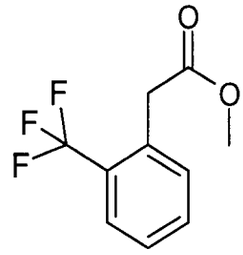
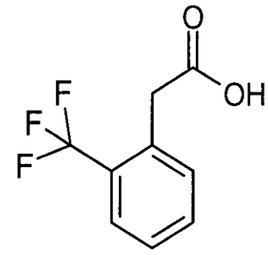
El siguiente ejemplo se sintetizó de manera análoga a la preparación del Ejemplo 5U, utilizando el correspondiente ácido como material de partida y metanol como disolvente.



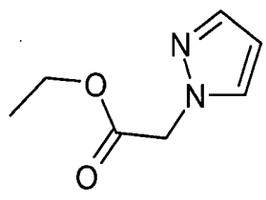
HPLC-MS (Método 1): tiempo de retención: 1,04 min

MS (ESI pos): m/z = 167 (M+H)+

Los siguientes ejemplos fueron sintetizados análogamente a la preparación del Ejemplo 5AM, utilizando los correspondientes ácidos como materiales de partida.

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 5AMA			1,52 (Método 1)	236 $(M+NH_4)^+$

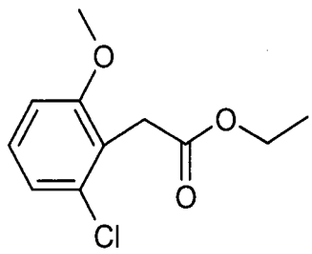
Ejemplo 5AN



Se disolvieron 6,0 g (88,5 mmol) de pirazol en 60 mL de DMSO y se añadieron 10,4 g (93 mmol) de *terc*-butilato de potasio en porciones, manteniendo la temperatura entre 20-25 °C. Se agitó la mezcla de reacción durante 10 min a temperatura ambiente. Se añadieron gota a gota 10,8 mL (98 mmol) de bromacetato de etilo, manteniendo la temperatura entre 25-35°C. Se agitó la mezcla de reacción durante 2 h a temperatura ambiente. Se añadió la mezcla de reacción a una solución acuosa

saturada de NaCl y se extrajo con acetato de etilo. Se secó la capa orgánica, se filtró, y se evaporó el filtrado a presión reducida. Se purificó el residuo por MPLC preparativa (SiO2, eluyente diclorometano/metanol 95/5). Se obtuvieron 10,4 g (38 %) del producto.

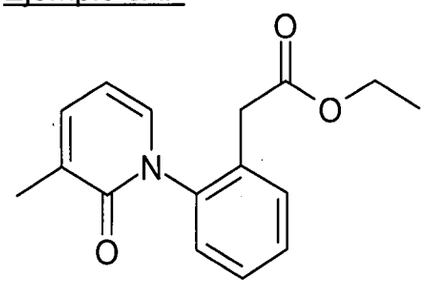
Ejemplo 5AO



Se mezclaron 1,83 g (7,7 mmol) del Ejemplo 4B con 60 mL de HCl 4 N y se enfriaron en un baño de hielo. Se añadió gota a gota una solución de 1,15 g (16,4 mmol) de nitrito de sodio en 13,5 mL de agua. Después de 10 min se añadió gota a gota una solución de 3,9 g (39,5 mmol) de cloruro de cobre(I) en 20 mL de HCl concentrado. Se dejó que la mezcla de reacción volviera a temperatura ambiente y se agitó durante 30 min. Se extrajo la mezcla con acetato de etilo. Se neutralizó la capa orgánica con carbonato de potasio, se filtró sobre celita y se extrajo el filtrado con agua. Se secó la capa orgánica, se filtró, y se evaporó el filtrado a presión reducida. Se obtuvieron 1,24 g (62 %) del producto.

HPLC-MS (Método 1): tiempo de retención: 1,60 min
MS (ESI pos): m/z = 229/231 (Cl) (M+H)+

Ejemplo 5AP

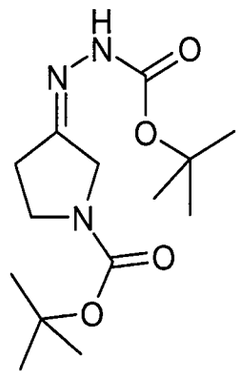


Se mezclaron, bajo argón, 1,00 g (4,11 mmol) del ejemplo 5U, 540 mg (4,95 mmol) de 3-metilpiridona y 80 mg (0,42 mmol) de yoduro de cobre-(I) con 5 mL de DMSO y

se añadieron 1,14 g (8,25 mmol) de carbonato de potasio y 120 mg (0,82 mmol) de 8-hidroxiquinolina. Se agitó la mezcla durante 48 h a 120 °C. Después de enfriar a temperatura ambiente se disolvió la mezcla en acetato de etilo y se lavó con HCl 1 M y solución saturada de cloruro de sodio. Se separó la fase orgánica, se secó y se evaporó. Se purificó el residuo por HPLC (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se evaporó el acetonitrilo y se extrajo el residuo con acetato de etilo. Se secó la fase orgánica y se evaporó para dar 633 mg (57 %) del producto deseado.

HPLC-MS (Método 1): tiempo de retención: 1,56 min
MS (ESI pos): m/z = 272 $(M+H)^+$

Ejemplo 6A



Se disolvieron 10 g (54 mmol) de 1-N-Boc-3-pirrolidinona en 50 mL de etanol y se añadieron 7,3 g (55,2 mmol) de carbazato de *terc*-butilo. Se agitó la mezcla de reacción a temperatura ambiente durante 2 h. Se evaporó el disolvente a presión reducida. Se purificó el residuo por MPLC preparativa (SiO_2, eluyente diclorometano/metanol 95/5). Se obtuvieron 18 g (89 %) del producto como un aceite.

HPLC-MS (Método 1): tiempo de retención: 1,35 min
MS (ESI neg.): m/z = 298 $(M-H)^-$

Ejemplo 6B

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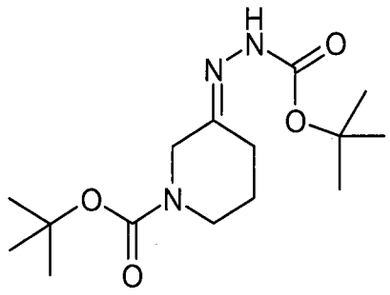
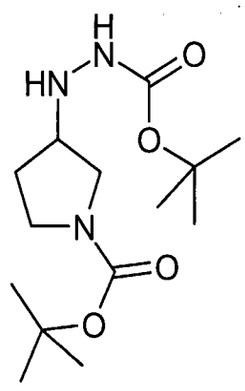
El siguiente ejemplo se sintetizó de manera análoga a la preparación del Ejemplo 6A, utilizando 1-N-Boc-3-piperidona como material de partida.



HPLC-MS (Método 1): tiempo de retención: 1,45 min

Ejemplo 7A, mezcla racémica



Se disolvieron 18 g (48 mmol) del Ejemplo 6A en 300 mL de metanol, se añadieron 2,5 g de Pd/C (al 10 %), y se hidrogenó la mezcla a temperatura ambiente (8 h, 344,8 kPa). Se filtró la mezcla de reacción y se lavó el residuo con metanol. Se evaporó el disolvente a presión reducida. Se obtuvieron 16 g de producto como un aceite incoloro y se utilizaron sin purificación adicional.

HPLC-MS (Método 1): tiempo de retención: 1,36 min

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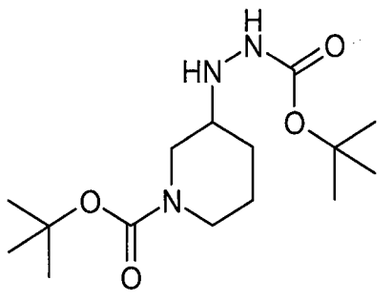
Ejemplo 7B, mezcla racémica

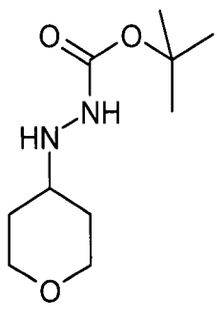
El siguiente ejemplo se sintetizó de manera análoga a la preparación del Ejemplo 7A, utilizando el Ejemplo 6B como material de partida.



HPLC-MS (Método 1): tiempo de retención: 1,42 min

MS (ESI pos): m/z = 316 (M+H)+

Ejemplo 7C

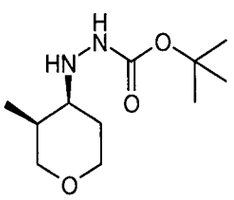
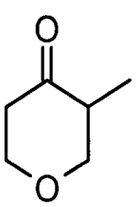
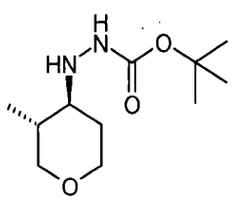
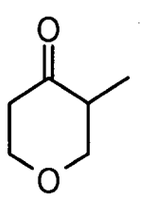
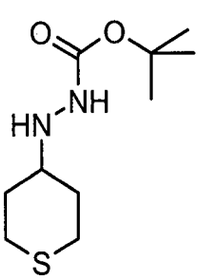
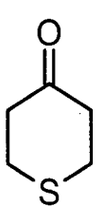


Se disolvieron 10 g (100 mmol) de tetrahidropiran-4-ona en 100 mL de metanol y se añadieron 14,5 g (110 mmol) de carbazato de *terc*-butilo. Se agitó la mezcla de reacción a temperatura ambiente durante 2 h. Se evaporó el disolvente a presión reducida. Se mezcló el residuo con 140 mL de ácido acético (50 %), se añadieron 6,9 g (110 mmol) de cianoborohidruro de sodio y se agitó la mezcla a temperatura ambiente durante la noche. Se neutralizó la mezcla de reacción con NaOH 4 M y se

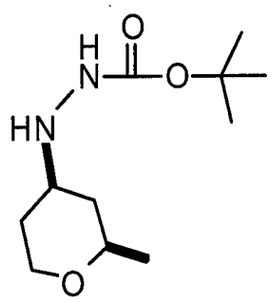
extrajo con diclorometano. Se lavó la capa orgánica con una solución acuosa saturada de hidrogenocarbonato de sodio y una solución acuosa saturada de cloruro de sodio. Se secó la capa orgánica sobre sulfato de sodio, se filtró, y se concentró el filtrado a presión reducida. Se obtuvieron 19 g (88 %) del producto como un sólido blanco.

MS (ESI pos): m/z = 217 (M+H)+

El siguiente ejemplo se sintetizó de manera análoga a la preparación del Ejemplo 7C utilizando la correspondiente cetona como material de partida.

	Estructura	material de partida: cetona	tiempo de retención [min]	MS m/z
Ejemplo 7CA mezcla cis, racémica			11,12 (Método 3A)	174 [EI, (M-56)$^+$]
Ejemplo 7CB mezcla trans, racémica			11,22 – (Método 3A)	174 [EI, (M-56)$^+$]
Ejemplo 7CC			0,99 (Método 1)	177 [ESI, (M-56+H)$^+$]

Ejemplo 7D



Mezcla cis-racémica

Una solución de 2-metil-tetrahidro-piran-4-ona (2,2 g, 19,7 mmol) en metanol (30 mL) se trató con carbazato de *terc*-butilo (2,6 g, 19,7 mmol) y se agitó durante 3 h a 20 °C. Por evaporación del disolvente se obtuvo un sólido blanco que se mezcló con 30 mL de ácido acético (al 50 % en agua), y se trató con cianoborohidruro de sodio (1,2 g, 19,7 mmol) en porciones. Se agitó la mezcla a 20 °C durante 16 h y después se neutralizó con NaOH 5 N y se extrajo con diclorometano. Se lavó la fase orgánica con una solución saturada de NaHCO3 y salmuera, se secó, se filtró y se evaporó para dar un sólido crudo. La separación de los diastereoisómeros se obtuvo por cromatografía rápida sobre SiO2 eluyendo con una mezcla de ciclohexano/acetato de etilo de polaridad creciente (de 7/3 a 1/1) para dar 1,85 g (41 %) de un sólido blanco.

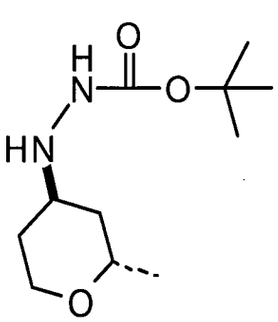
Rf: 0,29 (hexano/acetato de etilo 1:1)

HPLC-MS (Método Grad_90_10_C8_ácido): tiempo de retención: 1,79 min

MS (ESI pos): m/z = 131 $(M-100+H)^+$

La configuración cis entre el grupo metilo y el carbazilo estuvo implicada por la correlación ROESY para H-2/H-4.

Ejemplo 7E



Mezcla trans-racémica

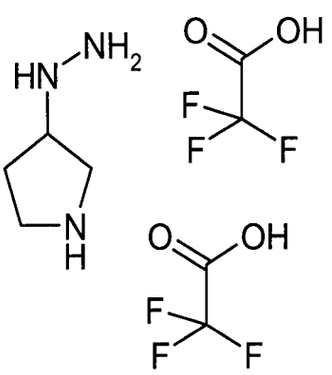
Se obtuvieron 0,7 g (16 %) de un aceite incoloro como el segundo producto a partir de la cromatografía rápida del Ejemplo 7D

Rf: 0,29 (hexano/acetato de etilo 1:1 teñido con el reactivo de Pancaldi)

HPLC-MS (Método Grad_90_10_C8_ácido): tiempo de retención: 1,96 min

MS (ESI pos): m/z = 131 $(M-100+H)^+$

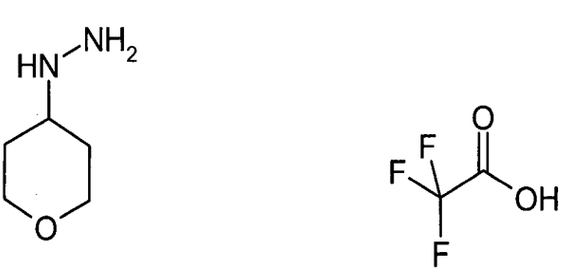
Ejemplo 8A, mezcla racémica



Se disolvieron 14 g (46,5 mmol) del Ejemplo 7A en 50 mL de diclorometano, se enfriaron en un baño de hielo y se añadieron 25 mL (325 mmol) de ácido trifluoroacético. Se agitó la mezcla de reacción durante 3 h a temperatura ambiente. Se evaporó el disolvente a presión reducida. Se purificó el residuo por MPLC preparativa (SiO_2, eluyente diclorometano/metanol 8/2). Se obtuvieron 12 g (78 %) del producto.

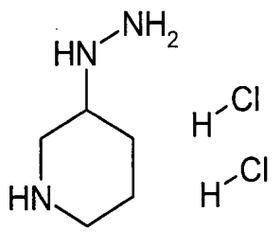
Ejemplo 8B

El siguiente ejemplo se sintetizó de manera análoga a la preparación del Ejemplo 8A, utilizando el Ejemplo 7C como material de partida.



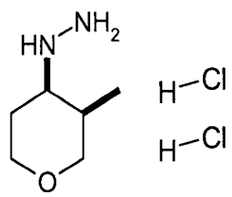
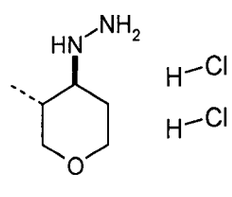
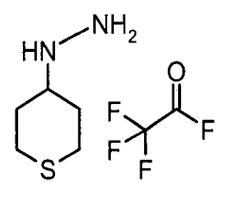
MS (ESI pos): m/z = 117 (M+H)+

Ejemplo 8C, mezcla racémica



Se disolvieron 13,0 g (37,1 mmol) del Ejemplo 7B en 5 mL de dioxano y se añadieron 93 mL (371 mmol) de ácido clorhídrico en dioxano (4 M). Se agitó la mezcla de reacción durante la noche a temperatura ambiente. Se añadieron 40 mL de éter dietílico y se agitó la mezcla durante 15 min a temperatura ambiente. Se filtró la mezcla de reacción. Se obtuvieron 7,0 g (100 %) del producto como un sólido blanco.

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del ejemplo 8C utilizando la correspondiente Boc-hidrazina como material de partida.

	Estructura	material de partida: Boc-hidrazina	MS m/z
Ejemplo 8CA mezcla cis, racémica		Ejemplo 7CA	131 $(M+H)^+$
Ejemplo 8CB mezcla trans, racémica		Ejemplo 7CB	131 $(M+H)^+$
Ejemplo 8CC		Ejemplo 7CC	133 $(M+H)^+$

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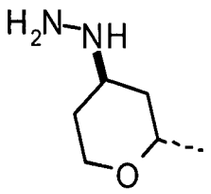
Ejemplo 8D



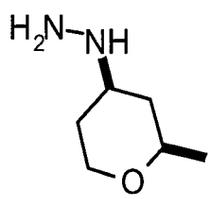
Mezcla trans-racémica

Una solución del Ejemplo 7E (700 mg, 3 mmol) en dioxano (5 mL) se trató con HCl 4 N en dioxano (15 mL, 60 mmol) y se agitó la mezcla a 20 °C durante 18 h. Se evaporó el disolvente para dar 560 mg (91 %) de un sólido pegajoso que se utilizó en la siguiente etapa sin purificación adicional.

HPLC-MS (Grad_C8_NH_4COOH_Lowmass): tiempo de retención: 0,67 min

MS (ESI pos): m/z = 131 (M+H)+

Ejemplo 8E



Mezcla cis-racémica

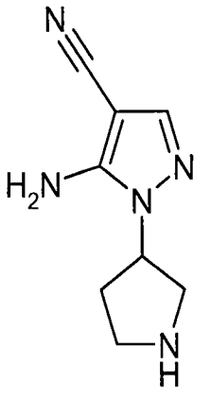
Análogamente a la preparación del Ejemplo 8D, se obtuvo el compuesto del epígrafe utilizando el Ejemplo 7D como material de partida.

Rendimiento: 68,3 %

HPLC-MS (Método Grad_C8_NH_4COOH_Lowmass): tiempo de retención: 0,70 min

MS (ESI pos): m/z = 131 (M+H)+

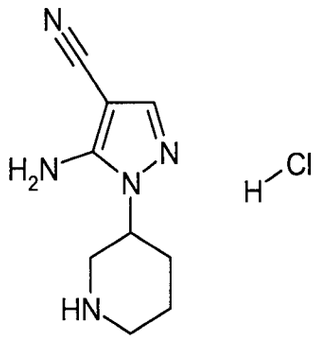
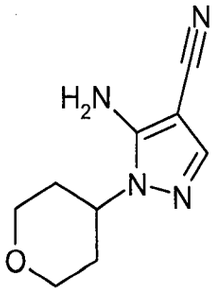
Ejemplo 9A, mezcla racémica

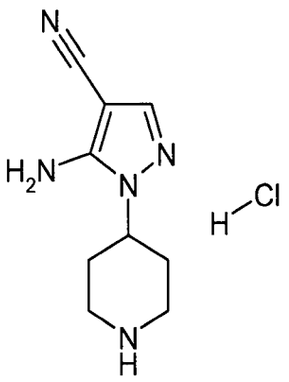
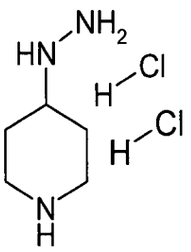
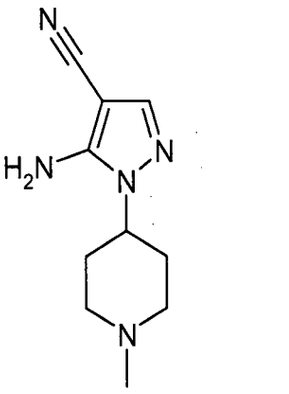
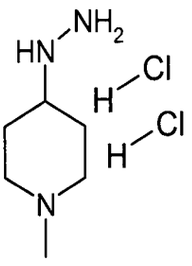
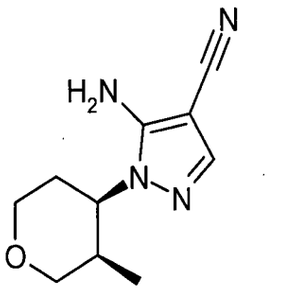
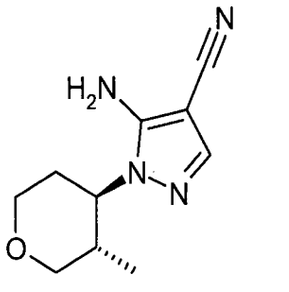


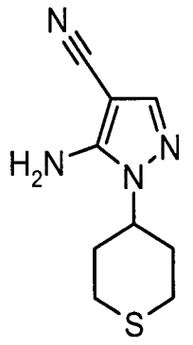
Se mezclaron 32,0 g (77,8 mmol) del Ejemplo 8A con 12,0 g (98,3 mmol) de etoximetilen-malonodinitrilo en 250 mL de etanol, y se añadieron 40 mL (288 mmol) de trietilamina. Se calentó la mezcla de reacción a 50 °C durante 2 h. Después de enfriar a temperatura ambiente se separó el disolvente a presión reducida. Se purificó el residuo por MPLC preparativa (SiO_2, eluyente diclorometano/metanol 8/2).

HPLC-MS (Método 1): tiempo de retención: 0,29 min

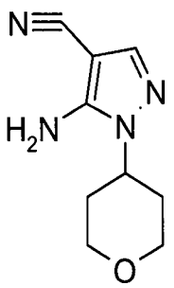
Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del ejemplo 9A, usando las correspondientes hidrazinas como materiales de partida:

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 9B mezcla racémica		Ejemplo 8C	0,59 (Método 1)	192 $(M+H)^+$
Ej. 9C		Ejemplo 8B	0,76 (Método 1)	193 $(M+H)^+$

Ej. 9D			0,32 (Método 1)	192 $(M+H)^+$
Ej. 9E			0,40 (Método 1)	206 $(M+H)^+$
Ejemplo 9EA mezcla cis, racémica		Ejemplo 8CA	1,90 Grad C8-NH_4CCOH	207 $(M+H)^+$
Ejemplo 9EB mezcla trans, racémica		Ejemplo 8CB	1,87 Grad C8-NH_4CCOH 1.87 GradC18 _NH4COOH	207 $(M+H)^+$

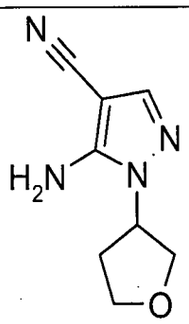
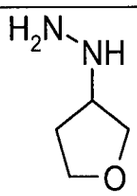
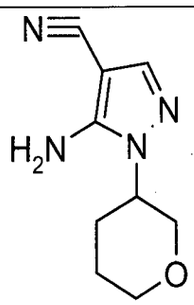
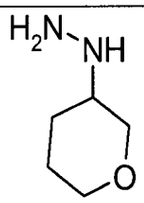
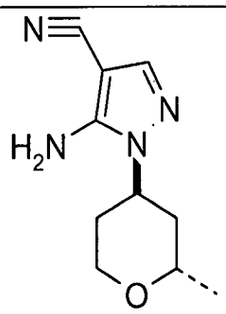
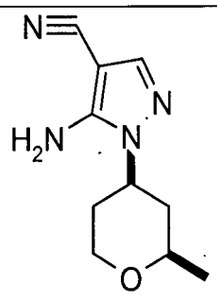
Ejemplo 9EC		Ejemplo 8CC	1,01 (Método 1)	209 $(M+H)^+$

Ejemplo 9F

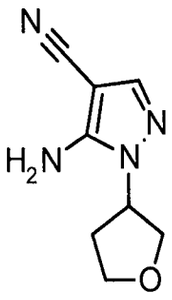


Se agitó a 50 °C durante 30 min una mezcla de 4,4 g (38 mmol) de (tetrahidro-piran-4-il)-hidrazina y 4,7 g (38 mmol) de etoximetilen-malononitrilo en 90 mL de etanol y 10,5 mL (103 mmol) de trietilamina. Después de enfriar a 20 °C se separó el disolvente a presión reducida y se trató el residuo con una mezcla de agua/diclorometano = 1/1. Se agitó la suspensión resultante durante 15 min y después se filtró para dar un sólido amarillo que se lavó seguidamente con diclorometano, agua y diclorometano. Se secó el sólido a 45 °C a presión reducida. Se obtuvieron 2,7 g (37 %) del compuesto del epígrafe como un sólido amarillo que se usó en la siguiente etapa sin purificación adicional.

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del ejemplo 9F, usando las correspondientes hidrazinas como materiales de partida:

	Estructura	material de partida: hidrazina	tiempo de retención [min]	MS m/z
Ejemplo 9G mezcla racémica			1,31 (Método Grad_90_10_C8_ácido)	179 $(M+H)^+$
Ejemplo 9H mezcla racémica			4,97 (Método 1E hidro)	193 $(M+H)^+$
Ejemplo 9I mezcla trans; racémica		Ejemplo 8D	2,14 (Método Grad_10_90_C8_ácido)	207 $(M+H)^+$
Ejemplo 9J mezcla cis; racémica		Ejemplo 8E	1,91 (Método Grad_10_90_C8_ácido)	207 $(M+H)^+$

Ejemplo 9GA (Enantiómero A)



Enantiómero A

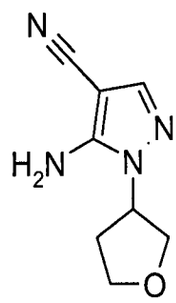
El Ejemplo 9G se sometió a separación quiral para aislar sus enantiómeros. El enantiómero denominado A, de estereoquímica desconocida pero sencilla se aisló utilizando las siguientes condiciones.

Cantidad suministrada	5 g
Columna quiral	Daicel Chiralpak AD 50 x 300 mm
Fase móvil	n-Hexano (60 %)/metil-*terc*-butil-éter (40 %) /Etanol (5 %) v/v
Caudal	20 mL/min
Detección	UV a 254 nm
Modo de inyección	continuo

Se obtuvo 1 g de enantiómero A.

Exceso enantiomérico 99,3 %; tiempo de retención 27,83 min; (método analítico: Quiral 3)

Ejemplo 9GB (Enantiómero B)



Enantiómero B

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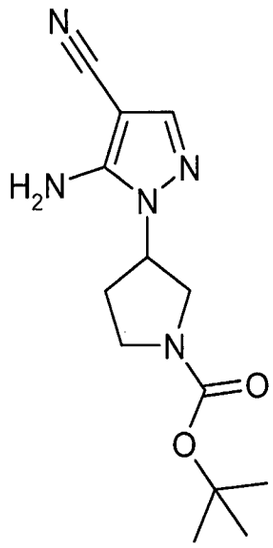
Se aisló utilizando las mismas condiciones que para el enantiómero A, obteniéndose 0,5 g; exceso enantiomérico 96,7 %; tiempo de retención: 30,94 min; (método analítico: Quiral 3).

Ejemplo 10A, mezcla racémica



Se mezclaron 4,0 g (22,6 mmol) del Ejemplo 9A con 60 mL de tetrahidrofurano, y se añadieron 5,7 g (30 mmol) de dicarbamato de di-*terc*-butilo. Se calentó la mezcla de reacción a 60 °C durante 5 h. Después de enfriar a temperatura ambiente se separó el disolvente a presión reducida. Se purificó el residuo por MPLC preparativa (SiO_2, eluyente diclorometano/metanol 9/1).

HPLC-MS (Método 1): tiempo de retención: 1,28 min

MS (ESI pos): m/z = 278 (M+H)+

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 10A, utilizando los correspondientes pirazoles como materiales de partida.

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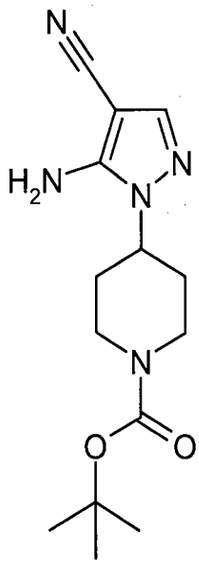
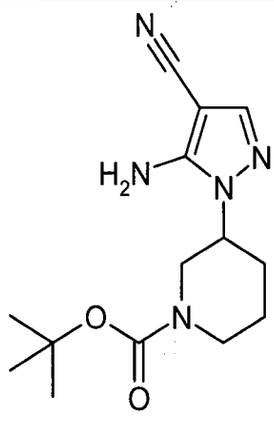
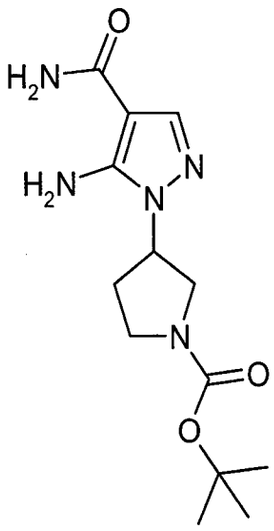
	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 10B		Ejemplo 9D	1,30 (Método 1)	292 $(M+H)^+$
Ej. 10C mezcla racémica		Ejemplo 9B	1,33 (Método 1)	292 $(M+H)^+$

Ejemplo 11A, mezcla racémica



Se disolvieron 2,4 g (8,96 mmol) del Ejemplo 10A en 30 mL de etanol. Se añadió lentamente a temperatura ambiente una solución de 10 mL (120 mmol) de peróxido de hidrógeno (al 35 % en agua) y 50 mL de amoníaco (al 25 % en agua) a lo largo de un periodo de 10 min. Se agitó la mezcla de reacción a temperatura ambiente durante 2 h. Se concentró cuidadosamente la solución hasta un volumen de 50 mL a presión reducida. Se formó un precipitado que se recogió por filtración. Se obtuvieron 1,3 g (50 %) del producto como un sólido.

HPLC-MS (Método 1): tiempo de retención: 1,08 min

MS (ESI pos): m/z = 296 (M+H)+

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 11A, utilizando los correspondientes pirazoles como materiales de partida.

	estructura	material de partida	tiempo de retención [min]	MS (ESI pos/neg, m/z)

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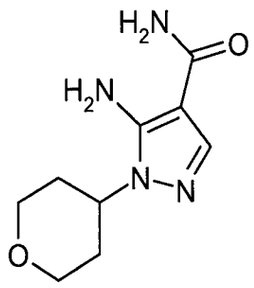
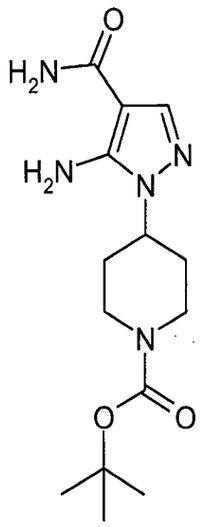
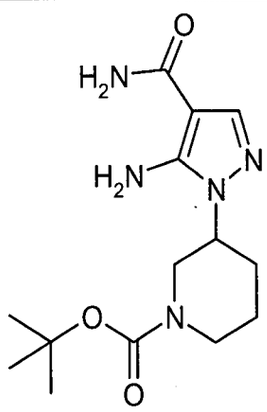
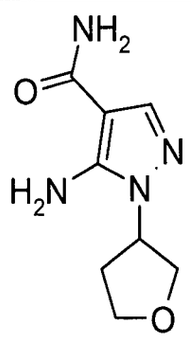
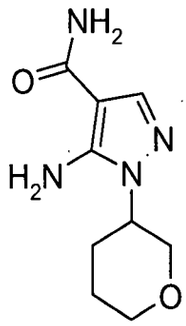
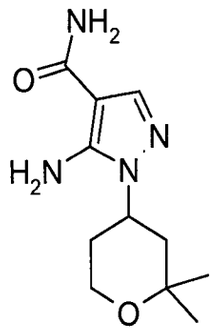
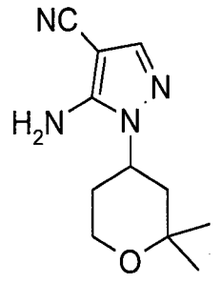
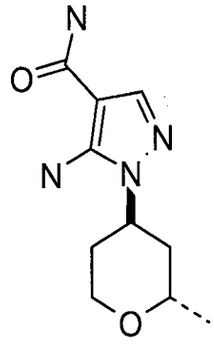
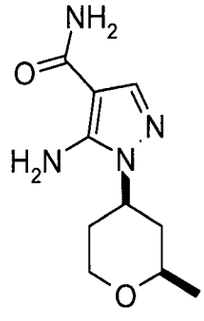
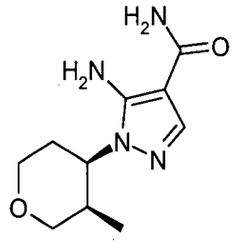
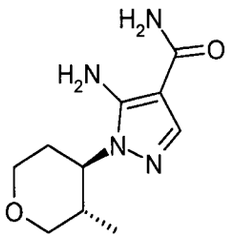
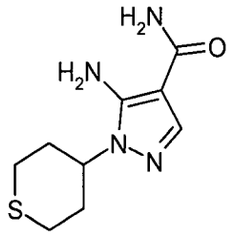
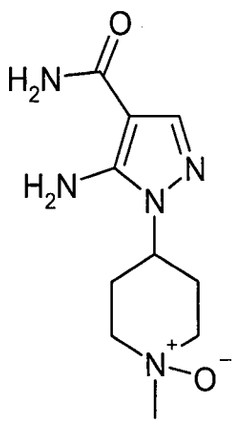
Ej. 11B		Ejemplo 9C	0,44 (Método 1)	211 $(M+H)^+$
Ej. 11C		Ejemplo 10B	1,12 (Método 1)	308 $(M-H)^-$
Ej. 11D mezcla racémica		Ejemplo 10C	1,13 (Método 1)	310/311 $(M+H)^+$ HPLC-MS

Ej. 11E mezcla racémica		Ejemplo 9G	2,39 (Método 2F)	197 $(M+H)^+$

Ej. 11F mezcla racémica		Ejemplo 9H	0,95 (Método Grad_C8_NH$_4$COOH)	211 $(M+H)^+$
Ej. 11G mezcla racémica			1,57 (Método Grad_C8_NH$_4$COOH)	339 $(M+H)^+$
Ej. 11H mezcla trans, racémica		Ejemplo 9I	1,27 (método Grad_90_10 _C8_ácido)	225 $(M+H)^+$
Ej. 11I mezcla cis, racémica		Ejemplo 9J	1,27 (método Grad_90_10 _C8_ácido)	225 $(M+H)^+$
Ejemplo 11IA mezcla cis, racémica		Ejemplo 9EA	1,11 (Método Grad_C8_NH 4COOH)	225 $(M+H)^+$

Ejemplo 11IB mezcla trans, racémica		Ejemplo 9EB	1,14 (Método Grad_C8_NH 4COOH)	225 $(M+H)^+$
Ejemplo 11IC		Ejemplo 9EC	0.80 min	227 $(M+H)^+$

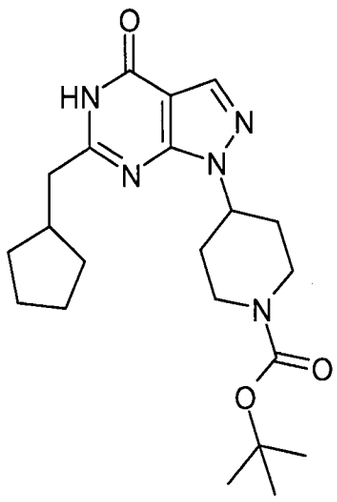
Ejemplo 11J, mezcla racémica



Se disolvieron 2,30 g (11,2 mmol) del Ejemplo 9E en 6 mL de dimetilsulfóxido. Bajo enfriamiento en hielo, se añadieron 8 mL (77,6 mmol) de peróxido de hidrógeno y 1,7 g (12,3 mmol) de carbonato de potasio. Se agitó entonces la mezcla de reacción durante 15 min a temperatura ambiente. Se enfrió la mezcla de reacción en un baño de hielo, se añadieron 100 mL de agua y se extrajo con diclorometano. Se evaporó la fase acuosa a presión reducida. Se mezcló el residuo con diclorometano y se filtró. Se obtuvieron 2,8 g (52 %) del producto como un sólido blanco.

HPLC-MS (Método 1): tiempo de retención: 0,24 min

Ejemplo 12A



Se disolvieron 660 mg (2,13 mmol) del Ejemplo 11C en 15 mL de etanol absoluto. Se añadieron 1,85 g (10,7 mmol) del Ejemplo 5AC y 430 mg (10,7 mmol) de hidruro de sodio (suspensión al 60 % en aceite mineral). Se calentó la mezcla de reacción a 150 ºC durante 30 min en un horno de microondas. El enfriamiento a temperatura ambiente fue seguido por evaporación del disolvente a presión reducida. Se purificó el residuo por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 320 mg (38 %) del producto como un sólido blanco.

HPLC-MS (Método 1): tiempo de retención: 1,61 min

MS (ESI pos): m/z = 402 (M+H)+

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 12A, utilizando los correspondientes pirazoles y ésteres como materiales de partida.

	Estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)

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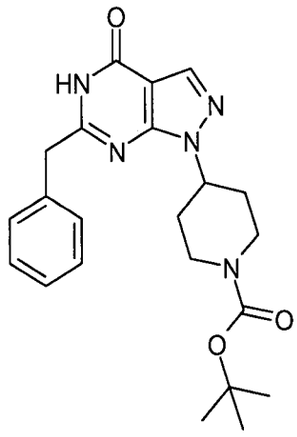
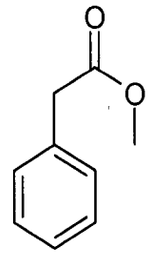
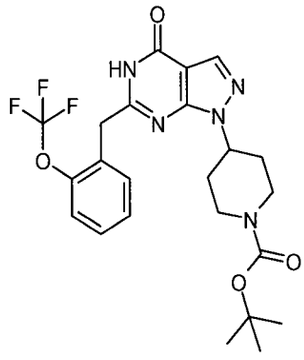
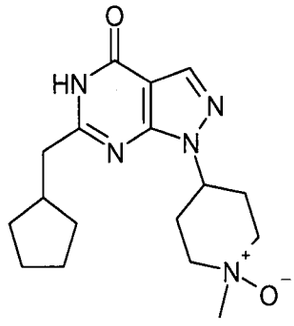
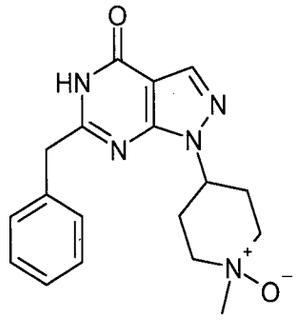
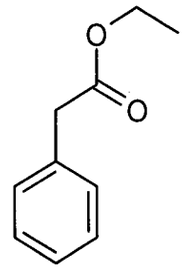
	Estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 12B		Ej. 11C		1,52 (Método 1)	410 $(M+H)^+$
Ej. 12C		Ej. 11C	Ejemplo 5AE	1,66 (Método 1)	492 $(M-H)^-$
Ej. 12D mezcla de estereoisó-meros		Ej. 11J	Ejemplo 5AC	1,02 (Método 1)	332 $(M+H)^+$
Ej. 12E mezcla de estereoisó-meros		Ej. 11J		0,96 (Método 1)	340 $(M+H)^+$

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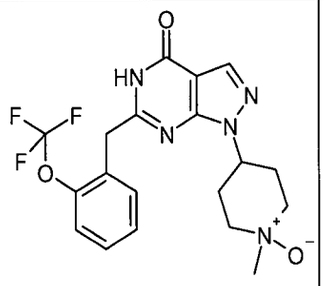
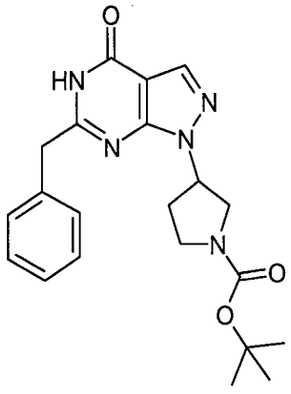
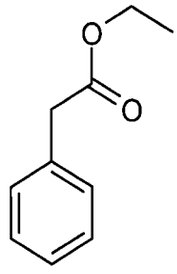
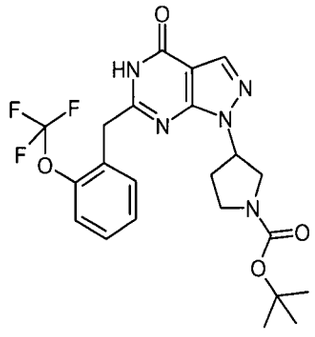
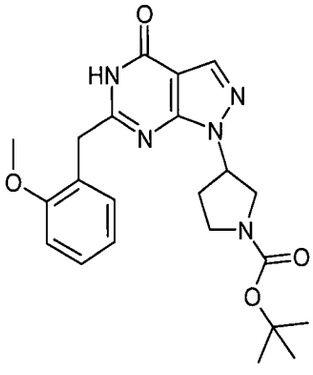
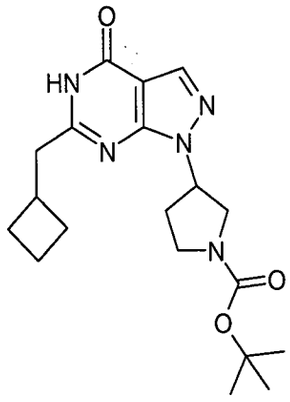
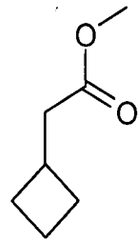
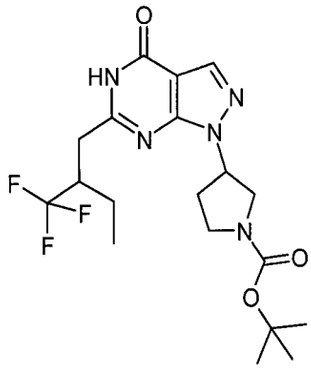
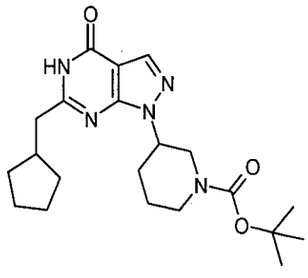
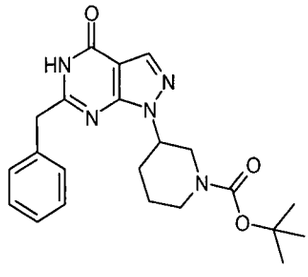
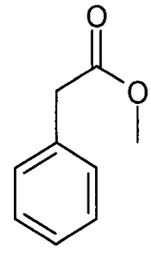
	Estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 12F mezcla de estereoisó-meros		Ej. 11J	Ejemplo 5AE	1,12 (Método 1)	424 $(M+H)^+$
Ej. 12G mezcla racémica		Ej. 11A		1,49 (Método 1)	396 $(M+H)^+$
Ej. 12H mezcla racémica		Ej. 11A	Ejemplo 5AE	1,62 (Método 1)	480 $(M+H)^+$
Ej. 12I mezcla racémica		Ej. 11A	Ejemplo 5AD	1,52 (Método 1)	426 $(M+H)^+$

	Estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 12J mezcla racémica		Ej. 11A		1,49 (Método 1)	374 $(M+H)^+$
Ej. 12K mezcla de estereoisó-meros		Ej. 11A	Ejemplo 5T	1,58 (Método 1)	428 $(M-H)^-$
Ej. 12L mezcla racémica		Ej. 11D	Ejemplo 5AC	1,65 (Método 1)	402 $(M+H)^+$
Ej. 12M mezcla racémica		Ej. 11D		1,55 (Método 1)	408 $(M+H)^+$

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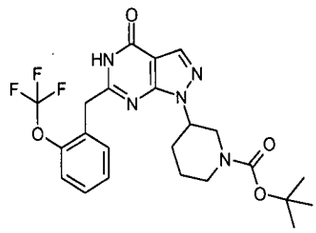
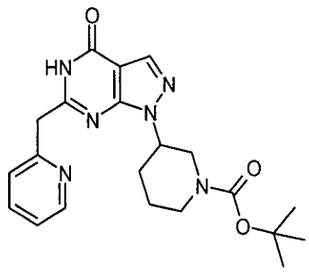
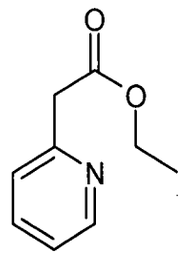
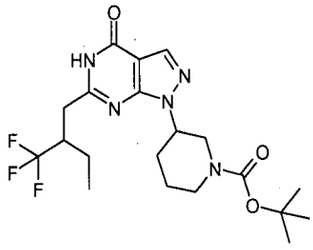
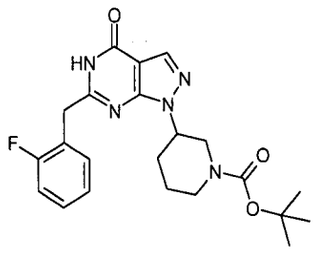
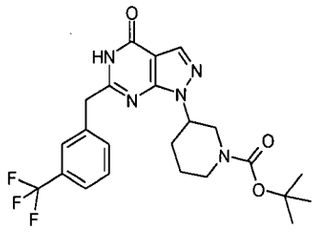
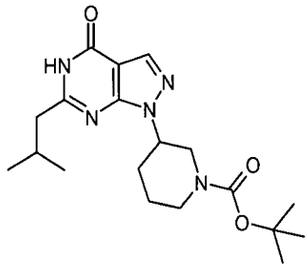
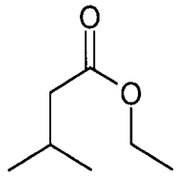
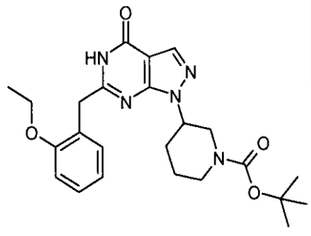
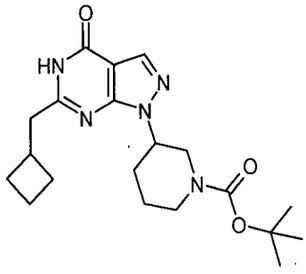
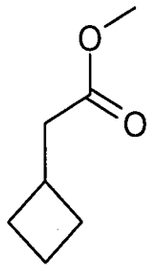
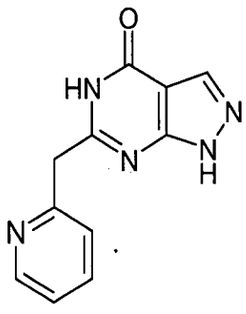
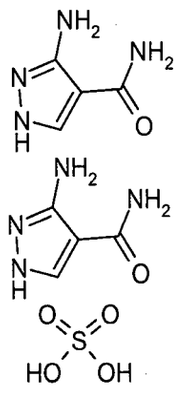
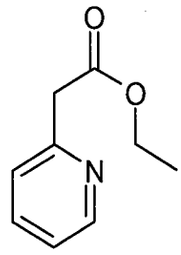
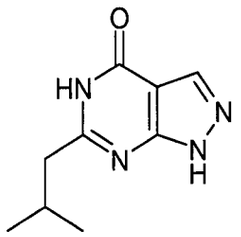
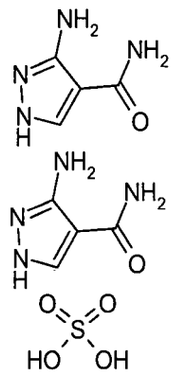
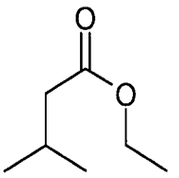
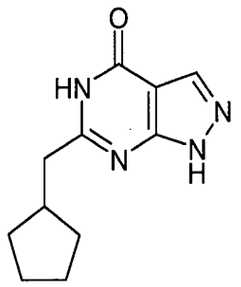
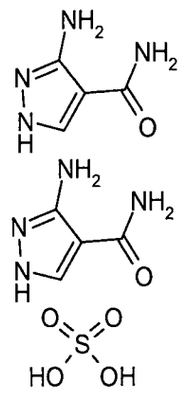
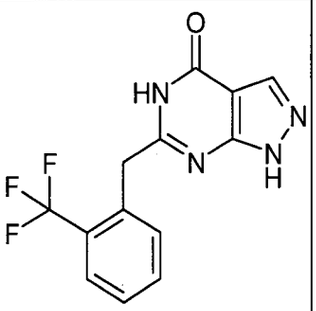
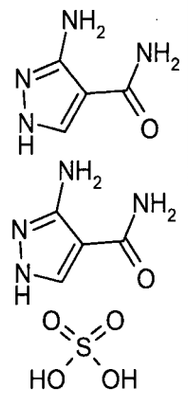
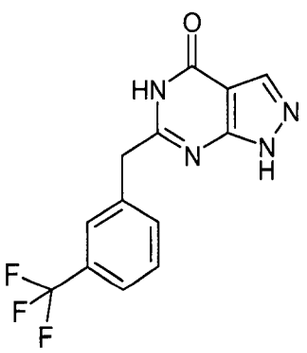
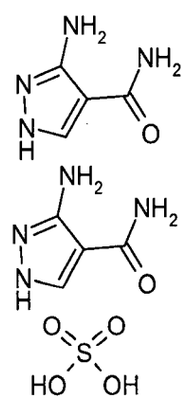
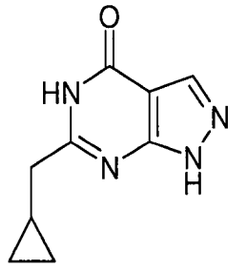
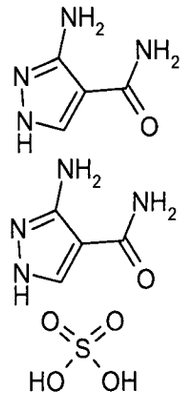
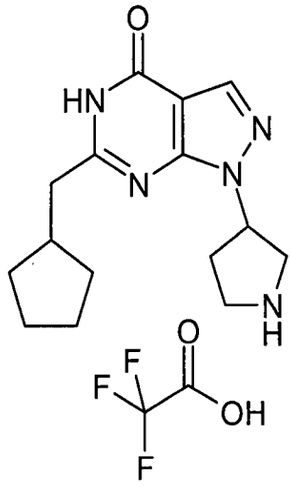
	Estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 12N mezcla racémica		Ej. 11D	Ejemplo 5AE	1,67 (Método 1)	494 $(M+H)^+$
Ejemplo 12O mezcla racémica		Ej. 11D		1,13 (Método 1)	411 $(M+H)^+$
Ej. 12P mezcla de estereoisó-meros		Ej. 11D	Ejemplo 5T	1,63 (Método 1)	444 $(M+H)^+$
Ej. 12Q mezcla racémica		Ej. 11D	Ejemplo 5AG	1,53 (Método 1)	428 $(M+H)^+$
Ej. 12R mezcla racémica		Ej. 11D	Ejemplo 5AH	1,66 (Método 1)	478 $(M+H)^+$

	Estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 12S mezcla racémica		Ej. 11D		1,51 (Método 1)	376 $(M+H)^+$
Ej. 12T mezcla racémica		Ej. 11D	Ejemplo 5AK	1,63 (Método 1)	454 $(M+H)^+$
Ej. 12U mezcla racémica		Ej. 11D		1,56 (Método 1)	388 $(M+H)^+$
Ej. 12V				1,77 (Método 2F)	228 $(M+H)^+$

	Estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 12W				6,96 (Método 2F)	193 $(M+H)^+$
Ej. 12X			Ejemplo 5AC	8,28 (Método 2F)	219 $(M+H)^+$
Ej. 12Y			Ejemplo 5AMA	9,15 (Método 2F)	295 $(M+H)^+$
Ejemplo 12Z			Ejemplo 5AH	9,54 (Método 2F)	295 $(M+H)^+$

	Estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ejemplo 12AA			Ejemplo 5ALA	6,48 (Método 2F)	191 $(M+H)^+$

Ejemplo 13A, mezcla racémica

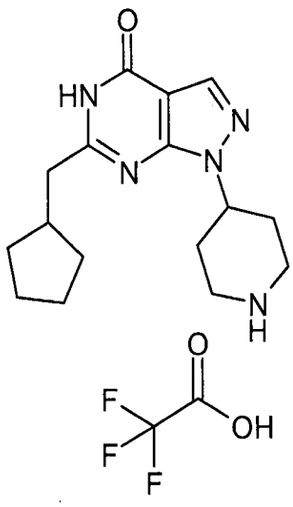


Se disolvieron 400 mg (1,35 mmol) del Ejemplo 11A en 8 mL de etanol absoluto, se añadieron 840 mg (5,4 mmol) del Ejemplo 5AC y 220 mg (5,5 mmol) de hidruro de sodio (suspensión al 60 % en aceite mineral). Se calentó la mezcla de reacción a 150 ºC durante 30 min en un horno de microondas. Después de enfriar a temperatura ambiente se acidificó la mezcla de reacción con ácido clorhídrico 4 N. Se separó el disolvente a presión reducida. Se purificó el residuo por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 250 mg (46 %) del producto como un sólido blanco.

HPLC-MS (Método 1): tiempo de retención: 0,93 min

MS (ESI pos): m/z = 288 (M+H)+

Ejemplo 13B

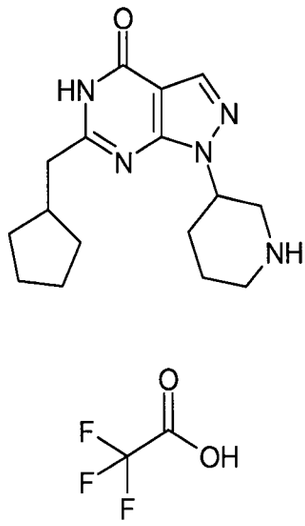
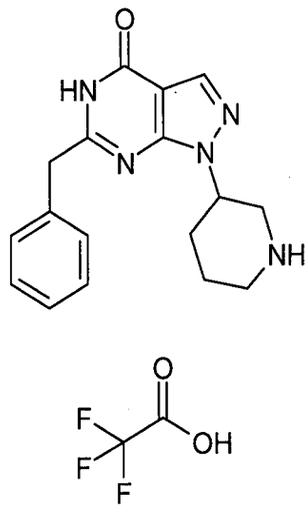
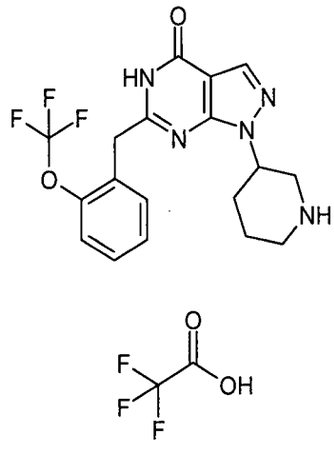


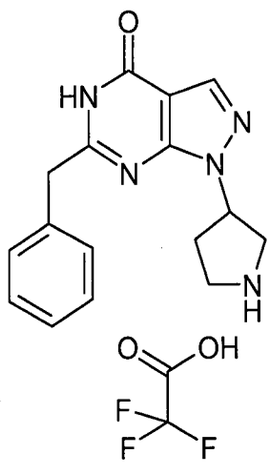
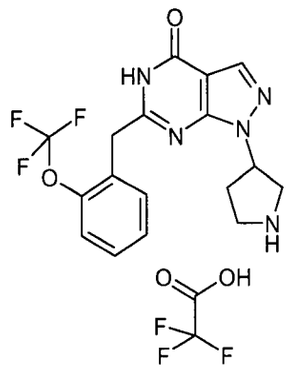
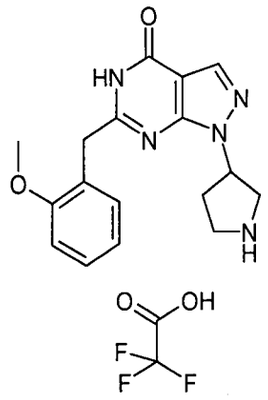
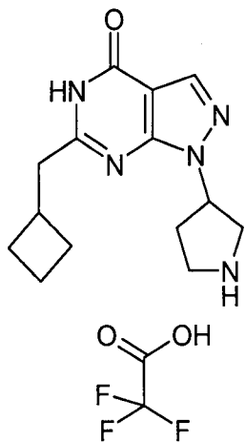
Se disolvieron 330 mg (0,82 mmol) del Ejemplo 12A en 3 mL de diclorometano y se añadió 1 mL de ácido trifluoroacético. Se agitó la mezcla de reacción a temperatura ambiente durante la noche. Se evaporó el disolvente a presión reducida. Se purificó el producto remanente por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 240 mg (70 %) del producto.

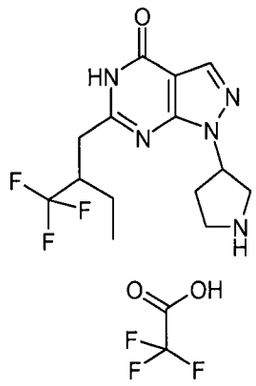
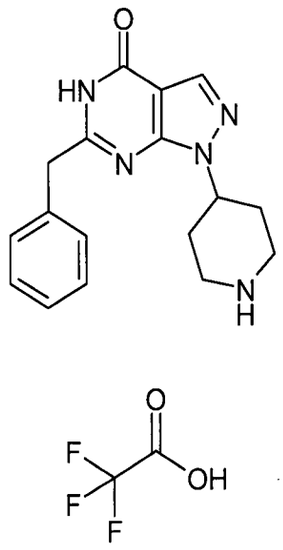
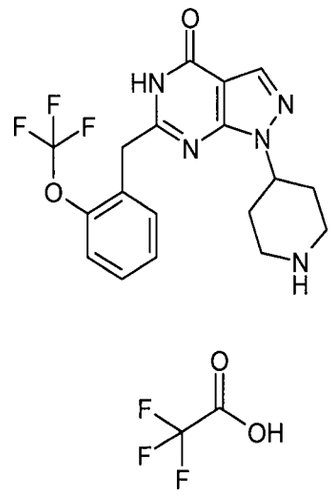
HPLC-MS (Método 1): tiempo de retención: 0,96 min

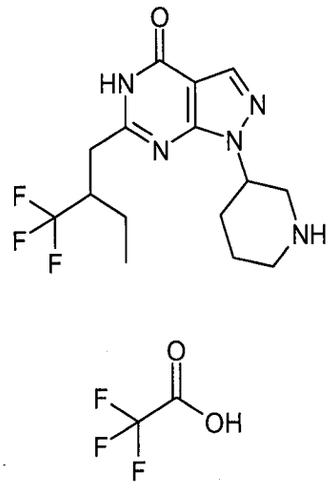
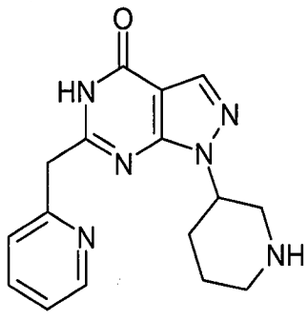
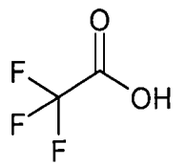
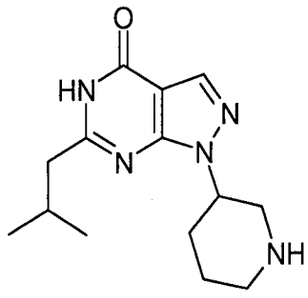
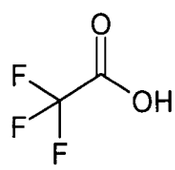
MS (ESI pos): m/z = 302 (M+H)+

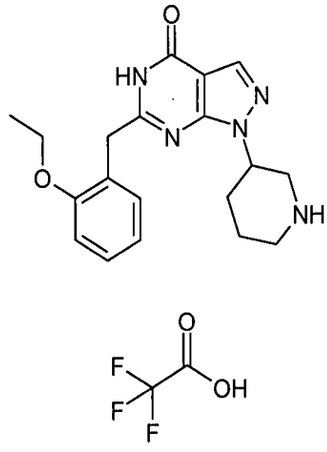
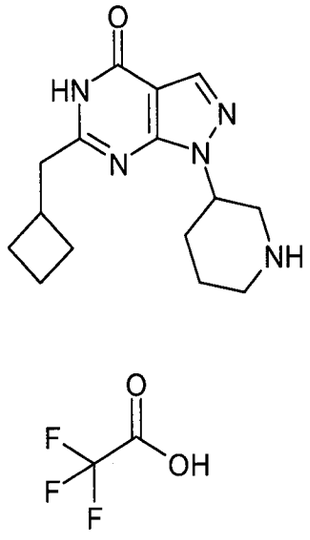
Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 13B, utilizando las correspondientes aminas protegidas con Boc como materiales de partida

	Estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 13C mezcla racémica		Ej. 12L	1,01 (Método 1)	302 $(M+H)^+$
Ej. 13D mezcla racémica		Ej. 12M	0,93 (Método 1)	310 $(M+H)^+$
Ej. 13E mezcla racémica		Ej. 12N	1,09 (Método 1)	394 $(M+H)^+$

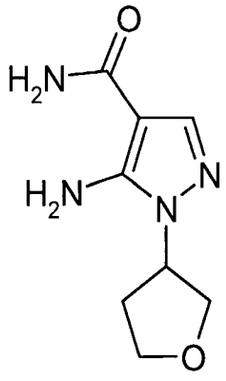
Ej. 13F mezcla racémica		Ej. 12G	0,92 (Método 1)	296 $(M+H)^+$
Ej. 13G mezcla racémica		Ej. 12H	1,08 (Método 1)	380 $(M+H)^+$
Ej. 13H mezcla racémica		Ej. 12I	0,96 (Método 1)	326 $(M+H)^+$
Ej. 13I mezcla racémica		Ej. 12J	0,89 (Método 1)	274 $(M+H)^+$

Ej. 13J mezcla racémica		Ej. 12K	1,0 (Método 1)	330 $(M+H)^+$
Ej. 13K		Ej. 12B	0,92 (Método 1)	310 $(M+H)^+$
Ej. 13L		Ej. 12C	1,07 (Método 1)	394 $(M+H)^+$

Ej. 13M mezcla de estereoisómeros		Ej. 12P	1,04 (Método 1)	344 $(M+H)^+$
Ej. 13N mezcla racémica	 	Ej. 12O	0,37 (Método 1)	319 $(M+H)^+$
Ej. 13O mezcla racémica	 	Ej. 12S	0,89 (Método 1)	276 $(M+H)^+$

Ej. 13P mezcla racémica		Ej. 12T	1,04 (Método 1)	354 $(M+H)^+$
Ej. 13Q mezcla racémica		Ej. 12U	0,94 (Método 1)	288 $(M+H)^+$

Ejemplo 15A:



Enantiómero A

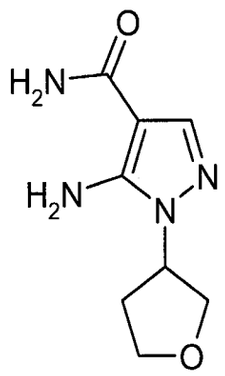
Se mezclaron 200 mg (1,12 mmol) del Ejemplo 9GA con 4,5 mL de solución de amoníaco (al 30 % en agua). Se calentó la mezcla de reacción a 130 °C durante 30

min en un horno de microondas. El enfriamiento a temperatura ambiente fue seguido por evaporación del disolvente a presión reducida. Se obtuvieron 180 mg (82 %) del producto.

GC-MS (Método 3A. 1): tiempo de retención: 12,62 min

$[M]^+$ = 196

Ejemplo 16A:



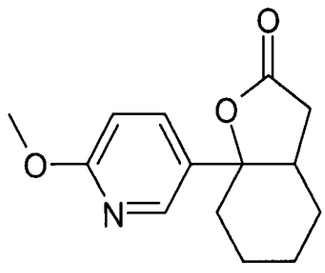
Enantiómero B

Se mezclaron 150 mg (0,84 mmol) del Ejemplo 9GB con 2,10 mL de solución de amoníaco (al 30 % en agua). Se calentó la mezcla de reacción a 130 °C durante 30 min en un horno de microondas. El enfriamiento a temperatura ambiente fue seguido por evaporación del disolvente a presión reducida. Se obtuvieron 100 mg (60 %) del producto.

GC-MS (Método 3A. 2): tiempo de retención: 12,59 min

$[M]^+$ = 196

Ejemplo 17A, mezcla de estereoisómeros

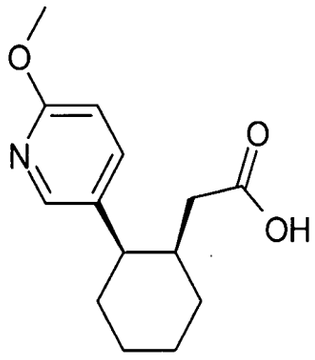


Una solución de 1,00 g (5,32 mmol) de 2-metoxi-5-bromopiridina en 10 mL de THF anhidro se enfrió a -78 °C y se añadió *n*-BuLi (3,66 mL, 5,85 mmol, 1,6 M en hexano). Después de 10 min a -78 °C se añadieron 1,18 g (6,38 mmol) de éster etílico del ácido 2-oxo-ciclohexil-acético y se calentó la mezcla a 25 °C. Se añadió agua (1 mL) y se concentró la mezcla a presión reducida. Se purificó el residuo por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 370 mg (28 %) del producto como un aceite.

HPLC-MS (Método 1): tiempo de retención: 1,23 min

MS (ESI pos): m/z = 248 (M+H)+

Ejemplo 18A, mezcla cis, racémica



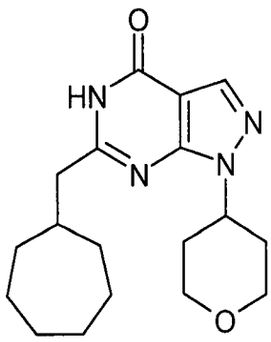
Se mezclaron 380 mg (1,54 mmol) del Ejemplo 17A con 5 mL de metanol, se añadieron 50 mg de Pd/C (al 10 %), y se hidrogenó la mezcla a temperatura ambiente (8h, 344,8 kPa). Se filtró la mezcla de reacción y se lavó el residuo con metanol. Se evaporó el disolvente a presión reducida. Se obtuvieron 340 mg (89 %) de producto como un aceite incoloro y se utilizaron sin purificación adicional.

HPLC-MS (Método 1): tiempo de retención: 1,01 min

MS (ESI pos): m/z = 250 (M+H)+

Realizaciones ilustrativas:

Ejemplo 1



Se disolvieron 100 mg (0,48 mmol) del Ejemplo 11B en 5 mL de etanol absoluto, se añadieron 400 mg (2,17 mmol) del Ejemplo 5V y 100 mg (2,5 mmol) de hidruro de sodio (suspensión al 60 % en aceite mineral). Se calentó la mezcla de reacción a 150 °C durante 30 min en un horno de microondas. El enfriamiento a temperatura ambiente fue seguido por evaporación del disolvente a presión reducida. Se purificó el residuo por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 29 mg (18 %) del producto como un sólido blanco.

HPLC-MS (Método 1): tiempo de retención: 1,08 min

MS (ESI pos): m/z = 331 (M+H)+

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 1, utilizando los correspondientes pirazoles y ésteres como materiales de partida.

	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)

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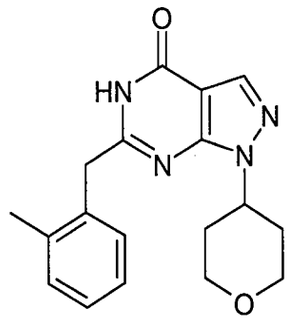
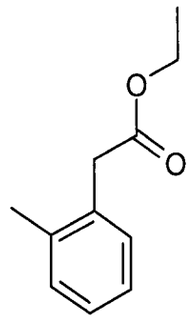
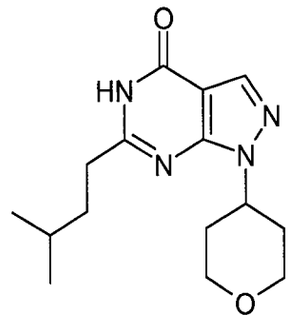
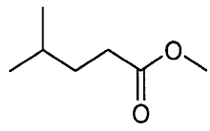
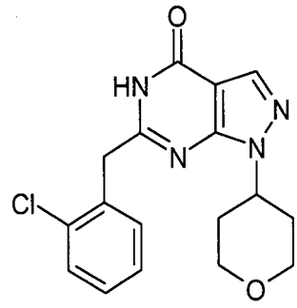
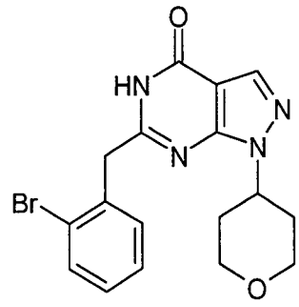
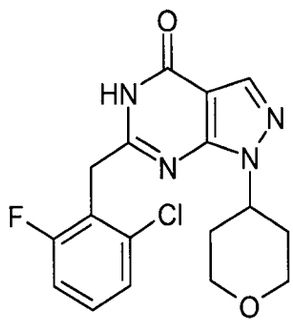
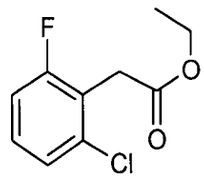
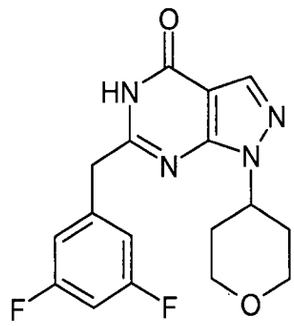
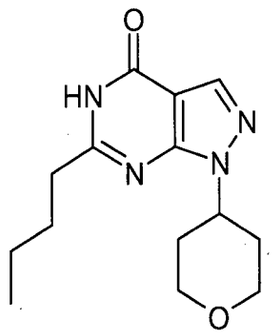
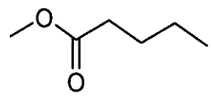
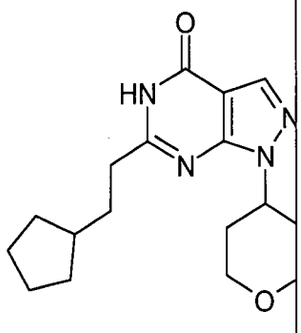
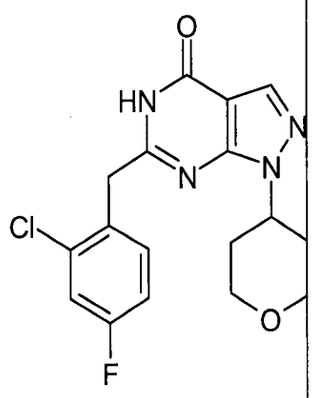
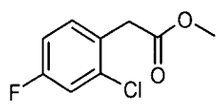
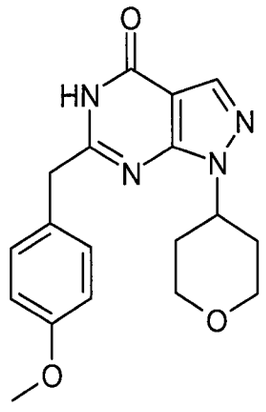
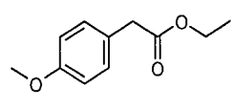
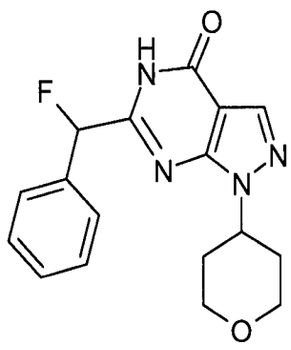
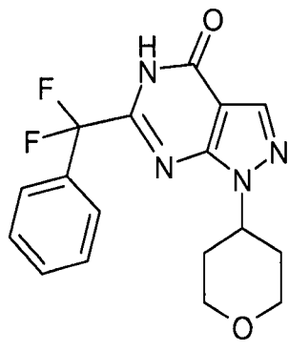
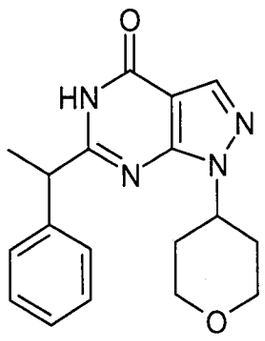
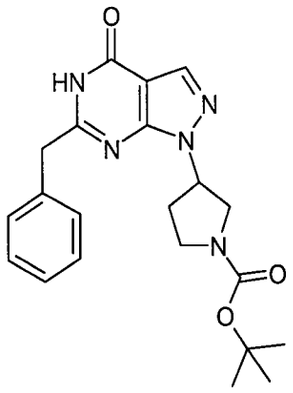
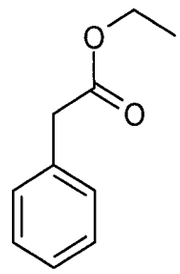
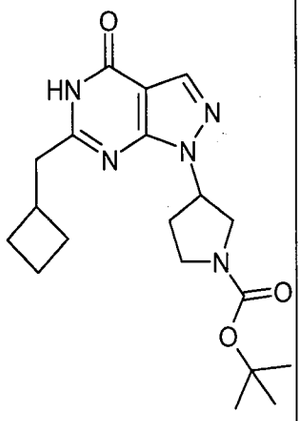
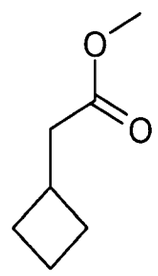
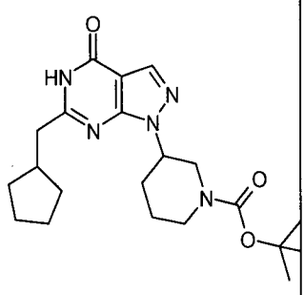
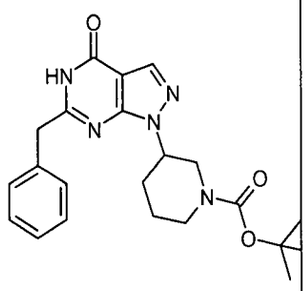
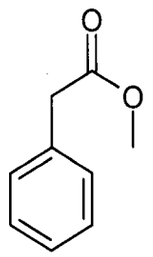
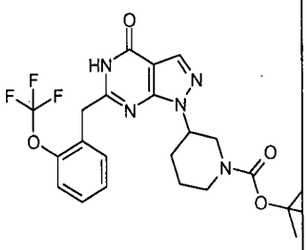
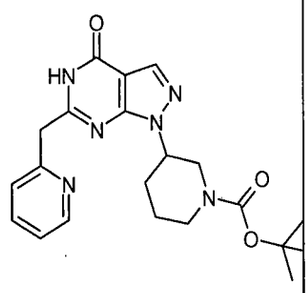
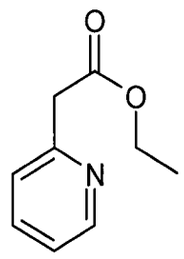
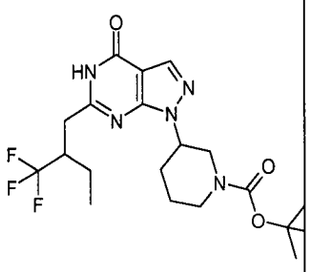
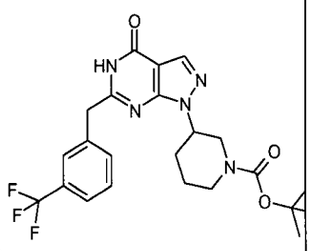
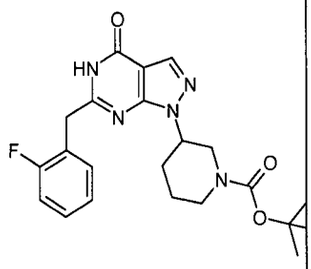
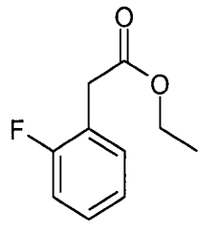
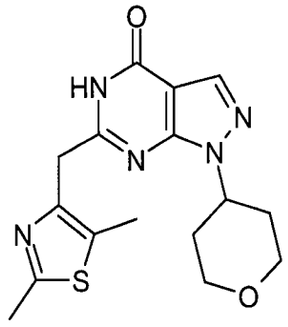
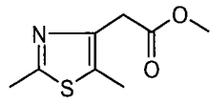
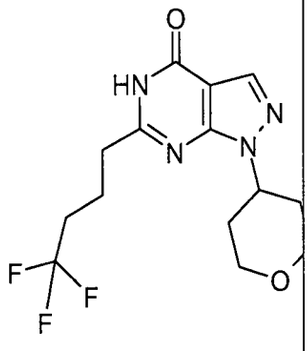
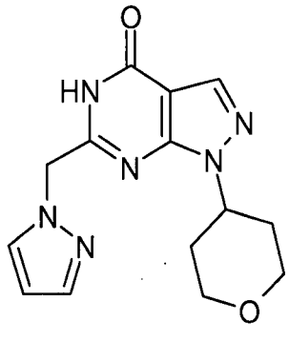
	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 2		Ejemplo 11B		1,27 (Método 1)	325 $(M+H)^+$
Ej. 3		Ejemplo 11B		1,22 (Método 1)	291 $(M+H)^+$
Ej. 4		Ejemplo 11B	Ejemplo 5Y	1,23 (Método 1)	345/347 (Cl) $(M+H)^+$
Ej. 5		Ejemplo 11B	Ejemplo 5U	1,29 (Método 1)	389/91 (Br) $(M+H)^+$

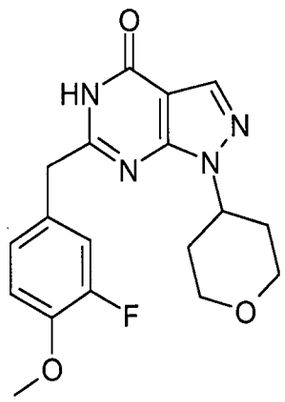
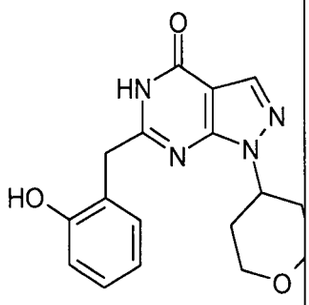
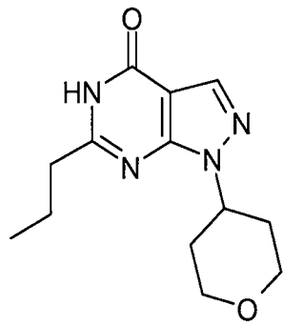
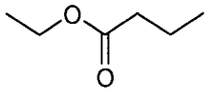
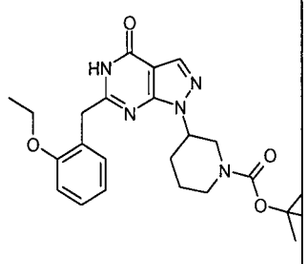
	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 6		Ejemplo 11B		1,28 (Método 1)	363/65 (Cl) $(M+H)^+$
Ej. 7		Ejemplo 11B	Ejemplo 5W	1,22 (Método 1)	345 $(M-H)^-$
Ej. 8		Ej. 11B		1,14 (Método 1)	277 $(M+H)^+$
Ej. 9		Ej. 11B	Ejemplo 5X	1,37 (Método 1)	317 $(M+H)^+$

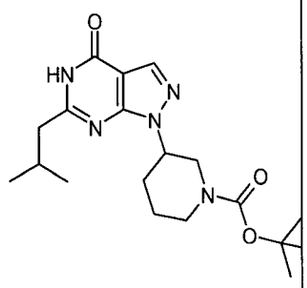
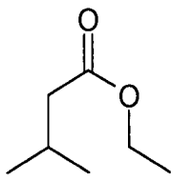
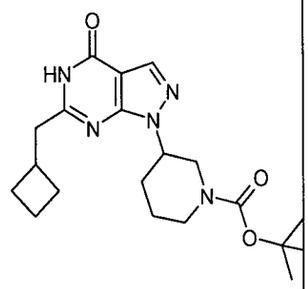
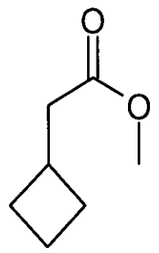
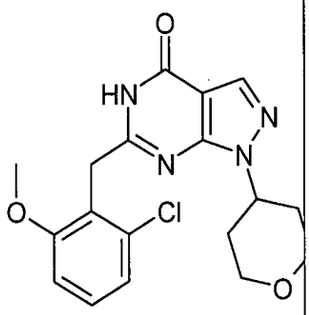
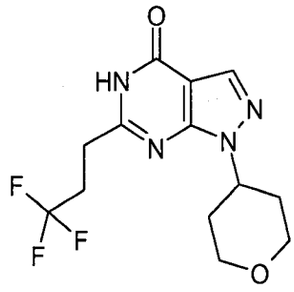
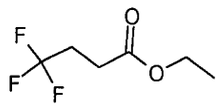
	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 10		Ej. 11B		1,30 (Método 1)	361/63 (Cl) $(M+H)^+$
Ej. 11		Ej. 11B		1,18 (Método 1)	341 $(M+H)^+$
Ej. 12 mezcla racé-mica		Ej. 11B	Ejemplo 5AA	1,44 (Método 1)	329 $(M+H)^+$
Ej. 13		Ej. 11B	Ejemplo 5AB	1,26 (Método 1)	347 $(M+H)^+$

	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 14 mezcla racé-mica		Ej. 11B	Ejemplo 5AF	1,28 (Método 1)	325 $(M+H)^+$
Ej. 15 mezcla racé-mica		Ej. 11A		1,49 (Método 1)	396 $(M+H)^+$
Ej. 16 mezcla racé-mica		Ej. 11A		1,49 (Método 1)	374 $(M+H)^+$
Ej. 17 mezcla racé-mica		Ej. 11D	Ejemplo 5AC	1,65 (Método 1)	402 $(M+H)^+$

	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 18 mezcla racé-mica		Ej. 11D		1,55 (Método 1)	408 $(M+H)^+$
Ej. 19 mezcla racé-mica		Ej. 11D	Ejemplo 5AE	1,67 (Método 1)	494 $(M+H)^+$
Ej. 20 mezcla racé-mica		Ej. 11D		1,13 (Método 1)	411 $(M+H)^+$
Ej. 21 mezcla racé-mica		Ej. 11D	Ejemplo 5T	1,63 (Método 1)	444 $(M+H)^+$
Ej. 22 mezcla racé-mica		Ej. 11D	Ejemplo 5AH	1,66 (Método 1)	478 $(M+H)^+$

	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 23 mezcla racé-mica		Ej. 11D		1,53 (Método 1)	428 $(M+H)^+$
Ej. 24		Ej. 11B		0,91 (Método 1)	346 $(M+H)^+$
Ej. 25		Ej. 11B	Ejemplo 5AI	1,17 (Método 1)	331 $(M+H)^+$
Ej. 26		Ej. 11B	Ejemplo 5AN	0,87 (Método 1)	301 $(M+H)^+$

	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 27		Ej. 11B	Ejemplo 5AJ	1,17 (Método 1)	359 $(M+H)^+$
Ej. 28		Ej. 11B	Ejemplo 5AM	1,08 (Método 1)	327 $(M+H)^+$
Ej. 29		Ej. 11B		1,02 (Método 1)	263 $(M+H)^+$
Ej. 30 mezcla racé-mica		Ej. 11D	Ejemplo 5AK	1,63 (Método 1)	454 $(M+H)^+$

	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 31 mezcla racé-mica		Ej. 11D		1,51 (Método 1)	376 $(M+H)^+$
Ej. 32 mezcla racé-mica		Ej. 11D		1,56 (Método 1)	388 $(M+H)^+$
Ej. 33		Ej. 11B	Ejemplo 5AO	1,29 (Método 1)	375/377 (Cl) $(M+H)^+$
Ej. 34		Ej. 11B		1,11 (Método 1)	317 $(M+H)^+$

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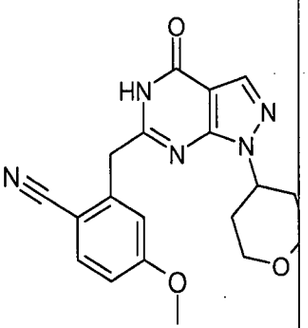
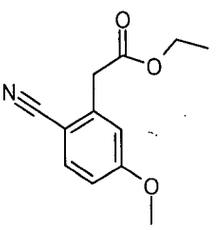
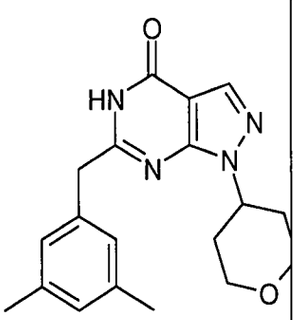
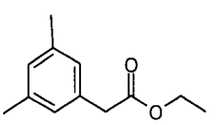
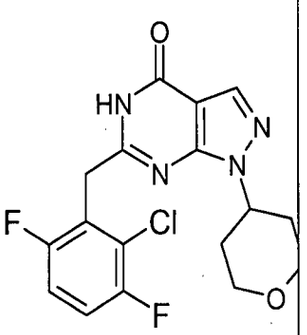
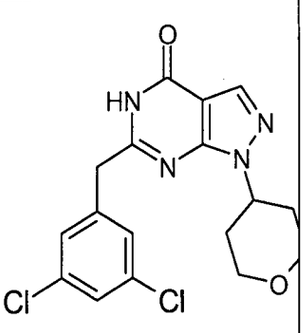
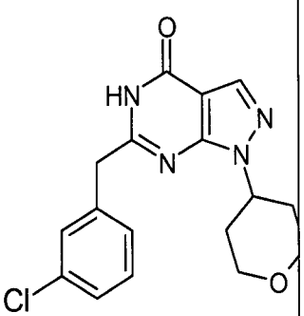
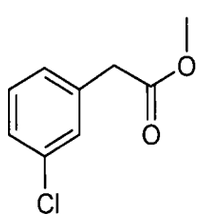
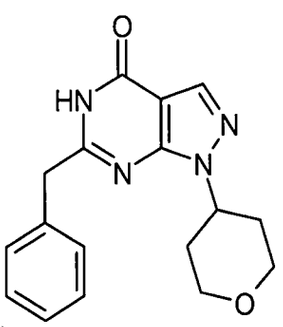
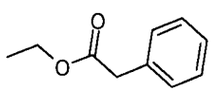
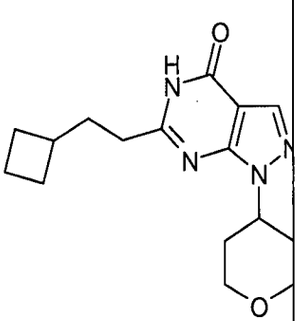
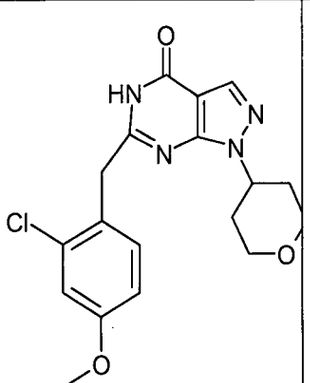
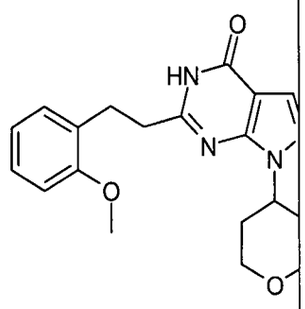
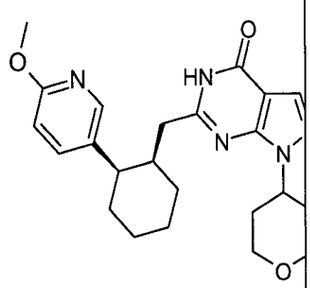
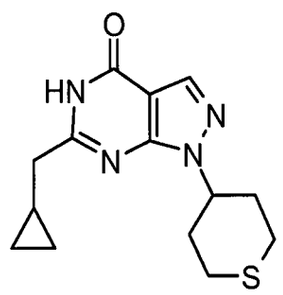
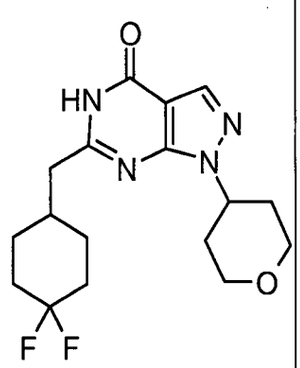
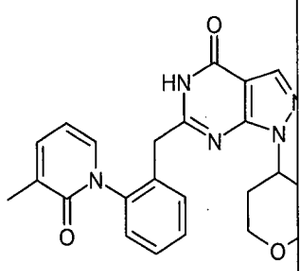
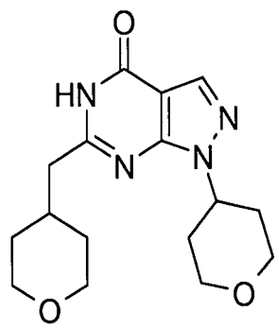
	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 35		Ej. 11B		1,17 (Método 1)	366 $(M+H)^+$
Ej. 36		Ej. 11B		1,36 (Método 1)	339 $(M+H)^+$
Ej. 37		Ej. 11B	Ejemplo 5AL	1,3 (Método 1)	381/383 (Cl) $(M+H)^+$
Ej. 38		Ej. 11B	Ejemplo 5Z	1,44 (Método 1)	379/381/383 (Cl_2) $(M+H)^+$

	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 39		Ej. 11B		1,28 (Método 1)	345/347 (Cl) $(M+H)^+$
Ej. 40		Ej. 11B		1,16 (Método 1)	311 $(M+H)^+$
Ej. 40-1		Ej. 11B	Ej. 5ALC	1,30 (Método 1)	303 $(M+H)^+$
Ej. 40-2		Ej. 11B	Ejemplo 5ALB	1,31 (Método 1)	375 $(M+H)^+$

	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 40-3		Ej. 11B	Ejemplo 5ALD	1,25 (Método 1)	355 $(M+H)^+$
Ej. 40-4 mezcla cis, racé-mica		Ej. 11B	Ej. 5HA	1,18 (Método 1)	424 $(M+H)^+$
Ej. 40-5		Ej. 11IC	Ej. 5ALA	1,24 (método 1)	291 $(M+H)^+$
Ej. 40-6		Ej. 11B	Ejemplo 5TA	1,22 (Método 1)	353 $(M+H)^+$

	estructura	material de partida: pirazol	material de partida: éster	tiempo de retención [min]	MS (ESI pos/neg, m/z)
Ej. 40-7		Ej. 11B	Ejemplo 5AP	1,35 (Método 1)	418 $(M+H)^+$

Ejemplo 41

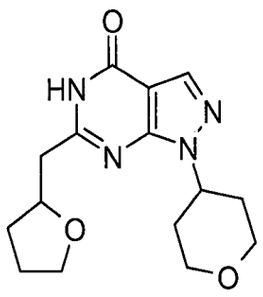
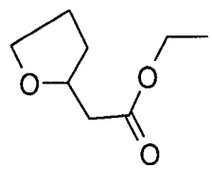
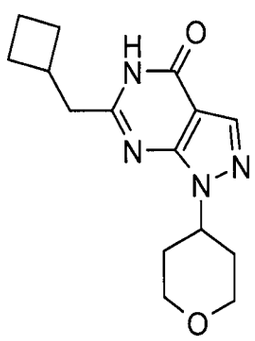
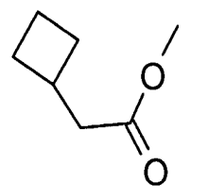
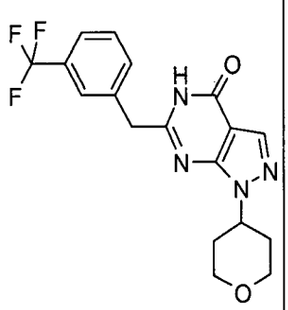
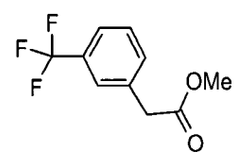
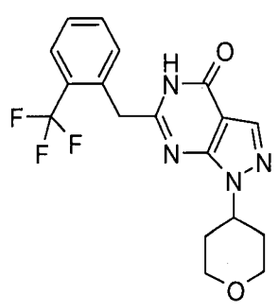
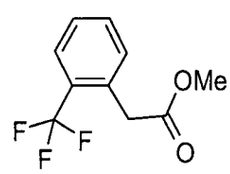


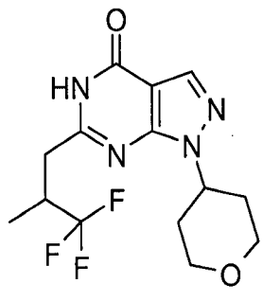
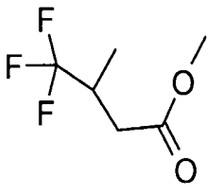
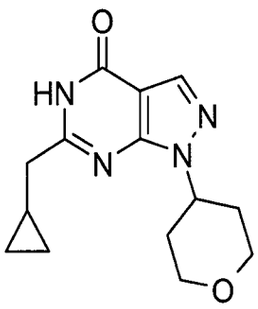
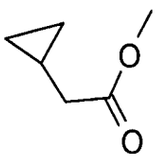
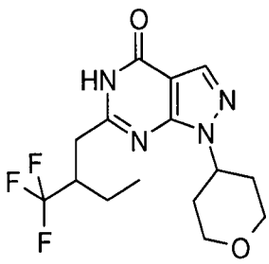
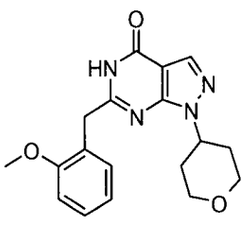
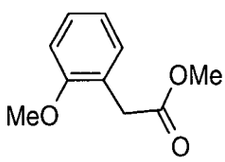
Se disolvieron 80 mg (0,38 mmol) del Ejemplo 11B en 1 mL de etanol absoluto, se añadieron 262 mg (1,52 mmol) de tetrahidropiran-4-il-acetato de etilo, y 45,1 mg (1,10 mmol) de hidruro de sodio (suspensión al 60 % en aceite mineral). Se calentó la mezcla de reacción a 150 °C durante 40 min en un horno de microondas. El enfriamiento a 20 °C fue seguido por evaporación del disolvente a presión reducida. Se trató el residuo con agua (10 mL), se acidificó con HCl (al 10 % en agua) y se extrajo dos veces con diclorometano (2 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró el filtrado a presión reducida. Se trituró el residuo con éter para dar 65 mg (53,7 %) del producto como un sólido blanco.

HPLC-MS (Método Grad_C8_NH_4COOH): tiempo de retención: 1,89 min

MS (ESI pos): m/z = 319 $(M+H)^+$.

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 41, utilizando las correspondientes pirazolil-carboxamidas y ésteres como materiales de partida:

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 42 mezcla racémica		Ej. 11B		2,02 (Método Grad_C8_ NH_4COOH)	305 $(M+H)^+$
Ej. 43		Ej. 11B		2,40 (Método Grad_C8_ NH_4COOH)	289 $(M+H)^+$
Ej. 44		Ej. 11B		3,06 (método Grad_C8_ NH_4COOH)	379 $(M+H)^+$
Ej. 45		Ej. 11B		3,04 (Método Grad_C8_ NH_4COOH	379 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
				)	
Ej. 46 mezcla racé-mica		Ej. 11B		2,77 (Método Grad_C8_ NH_4COOH)	331 $(M+H)^+$
Ej. 47		Ej. 11B		2,21 (Método Grad_C8_ NH_4COOH)	275 $(M+H)^+$
Ej. 48 mezcla racé-mica		Ej. 11B	Ej. 5T	2,84 (Método Grad_C8_ NH_4COOH)	345 $(M+H)^+$
Ej. 49		Ej. 11B		2,57 (Método Grad_C8_ NH_4COOH)	341 $(M+H)^+$

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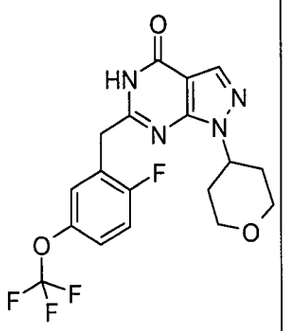
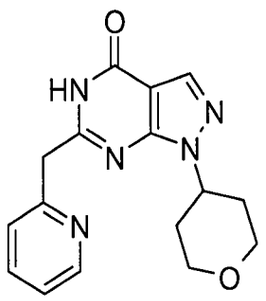
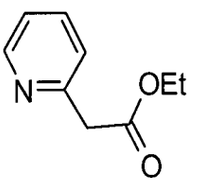
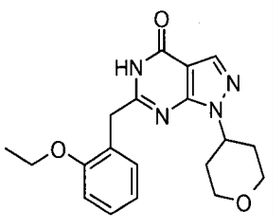
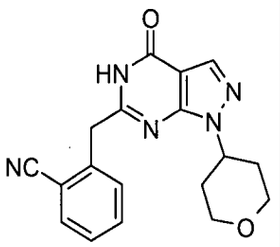
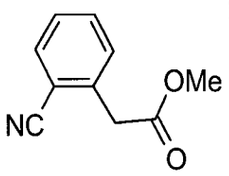
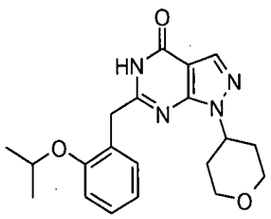
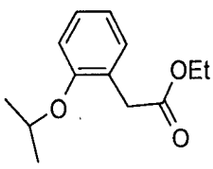
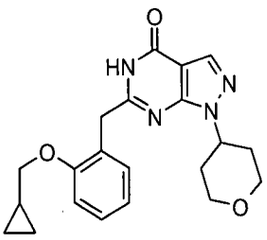
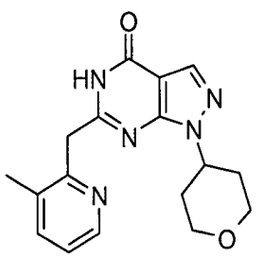
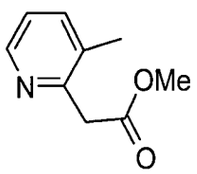
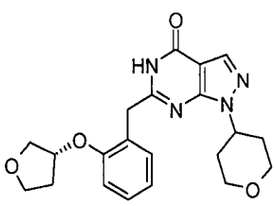
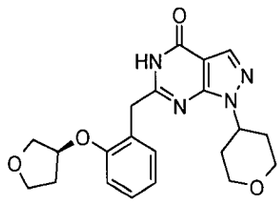
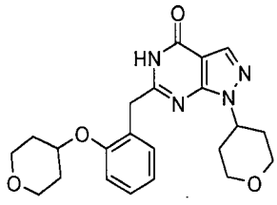
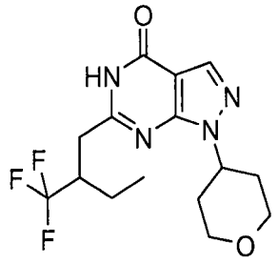
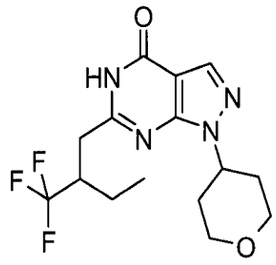
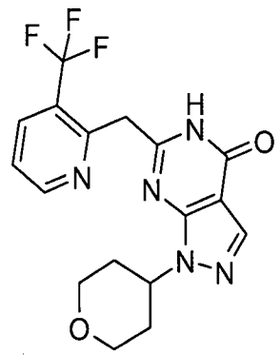
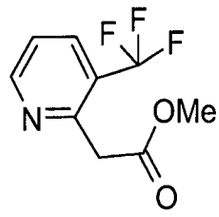
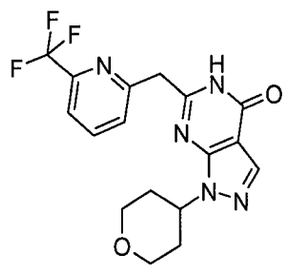
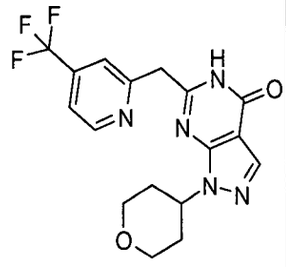
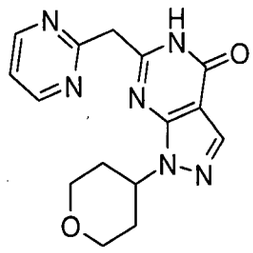
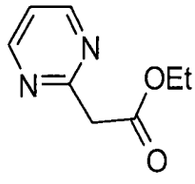
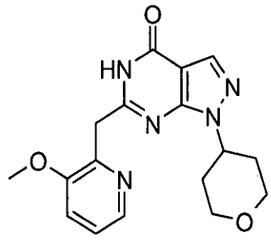
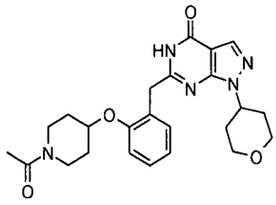
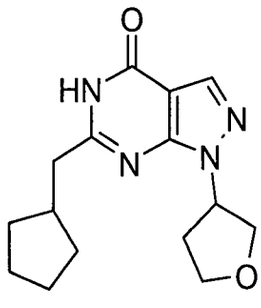
	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 50		Ej. 11B	Ej. 5E	3,02 (Método Grad_C8_ NH_4COOH)	413 $(M+H)^+$
Ej. 51		Ej. 11B		5,97 (Método 1E hidro)	312 $(M+H)^+$
Ej. 52		Ej. 11B	Ej. 5AK	2,75 (Método Grad_C8_ NH_4COOH)	355 $(M+H)^+$
Ej. 53		Ej. 11B		2,75 (Método Grad_C8_ NH_4COOH)	336 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 54		Ej. 11B		3,15 (Método Grad_C8_ NH_4COOH)	369 $(M+H)^+$
Ej. 55		Ej. 11B	Ej. 5K	3,21 (Método Grad_C8_ NH_4COOH)	381 $(M+H)^+$
Ej. 56		Ej. 11B		6,52 (Método 1E hidro)	326 $(M+H)^+$
Ej. 57 Enantiómero R		Ej. 11B	Ej. 5M	2,64 (Método Grad_C8_ NH_4COOH)	397 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 58 Enantiómero S		Ej. 11B	Ej. 5L	2,64 (Método Grad_C8_ NH_4COOH)	397 $(M+H)^+$
Ej. 60		Ej. 11B	Ej. 5O	2,78 (Método Grad_C8_ NH_4COOH)	411 $(M+H)^+$
Ej. 61 Enantiómero A		Ej. 11B	Ej. 5A	2,68 (Método Grad_C8_ NH_4COOH) 15,32 (Quiral 1)	345 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 62 Enantiómero B		Ej. 11B	Ej. 5D	2,68 (Método Grad_C8_ NH_4COOH) 18,74 (Quiral 1)	345 $(M+H)^+$
Ej. 63		Ej. 11B		9,37 (Método 2F)	380 $(M+H)^+$
Ej. 64		Ej. 11B	Ej. 5S	6,75 (Método 1E hidro)	380 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 65		Ej. 11B	Ej. 5R	9,45 (Método 2F)	380 $(M+H)^+$
Ej. 66		Ej. 11B		6,70 (Método 2F)	313 $(M+H)^+$
Ej. 67		Ej. 11B	Ej. 5Q	2,38 (Método Grad_C8_ NH_4COOH)	342 $(M+H)^+$
Ej. 68		Ej. 11B	Ej. 5I	1,95 (Método Grad_C8_ NH_4COOH)	452 $(M+H)^+$
Ej. 69 mezcla racé-mica		Ej. 11E	Ej. 5AC	7,30 (Método 1E)	289 $(M+H)^+$

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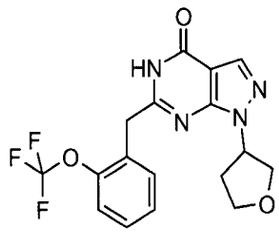
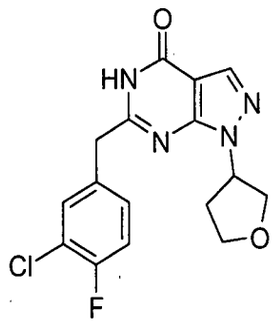
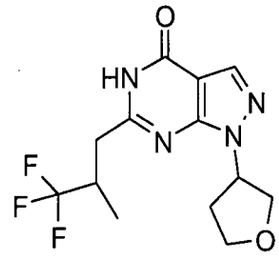
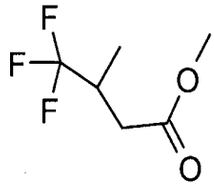
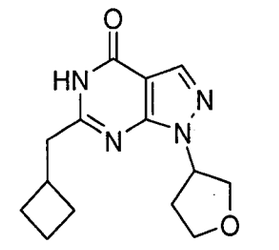
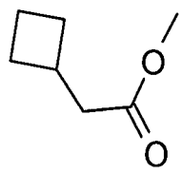
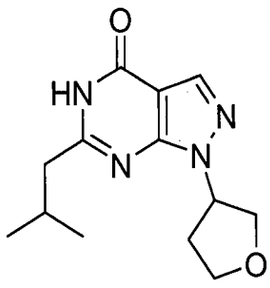
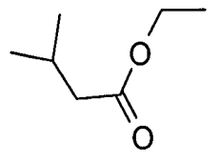
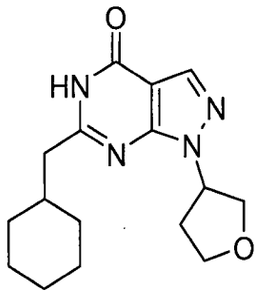
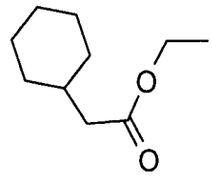
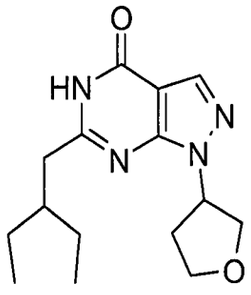
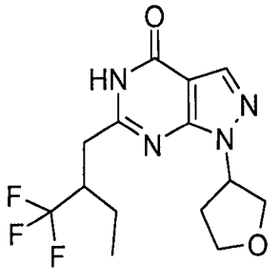
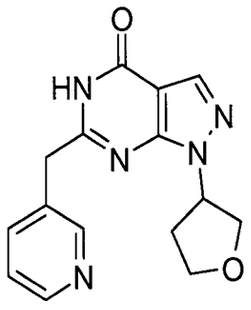
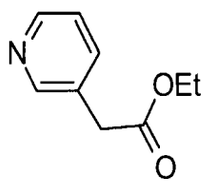
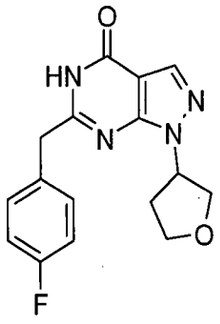
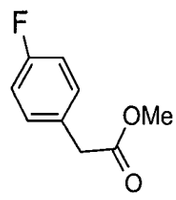
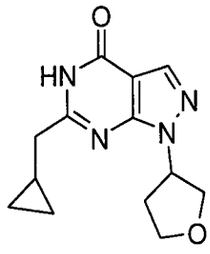
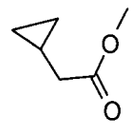
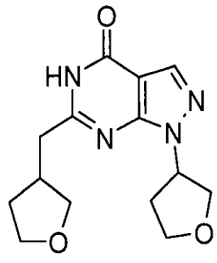
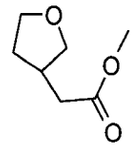
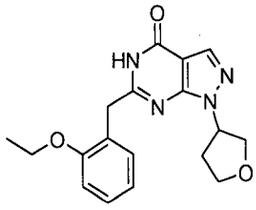
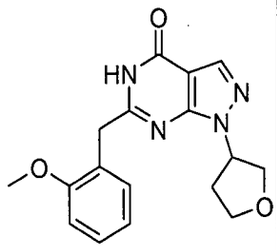
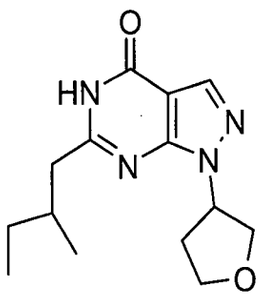
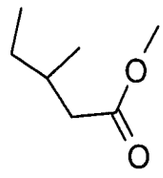
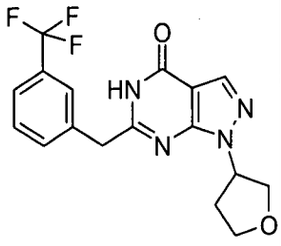
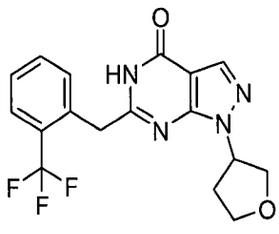
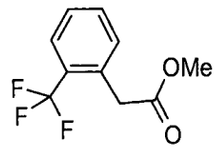
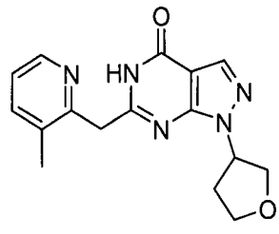
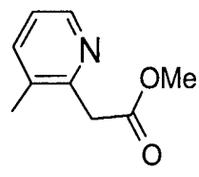
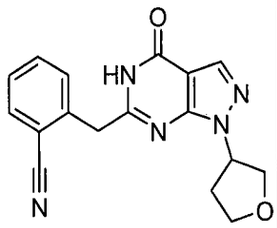
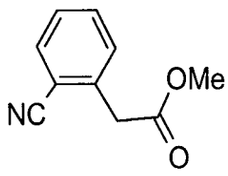
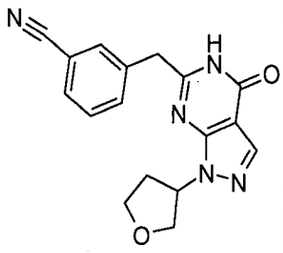
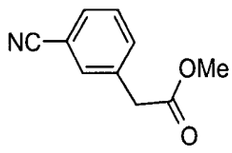
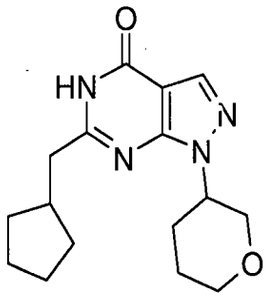
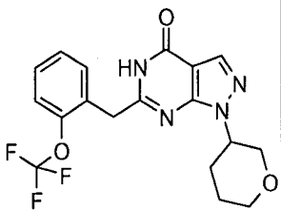
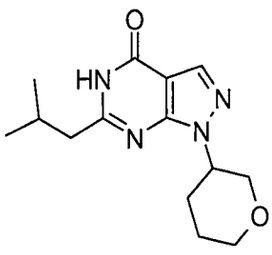
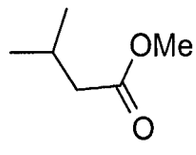
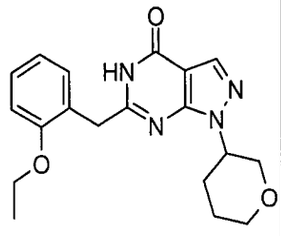
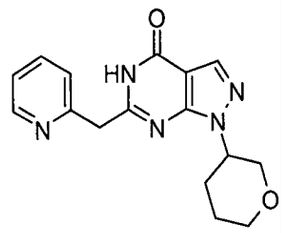
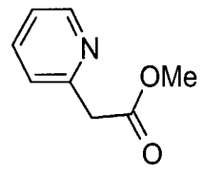
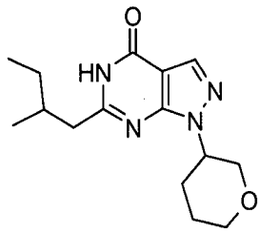
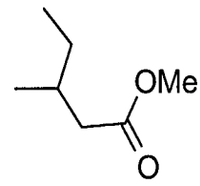
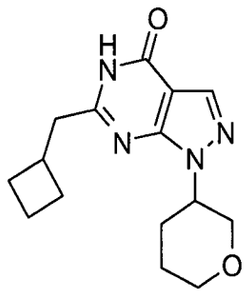
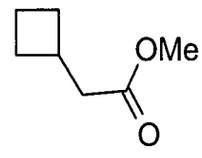
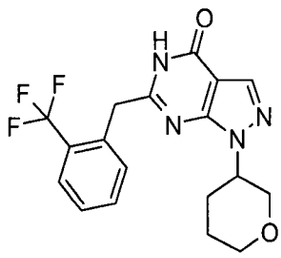
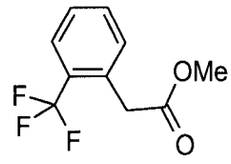
	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 70 mezcla racé-mica		Ej. 11E	Ej. 5AE	7,70 (Método 1E fusión)	381 $(M+H)^+$
Ej. 71 mezcla racé-mica		Ej. 11E	Ej. 5F	7,68 (Método 1E fusión)	349 $(M+H)^+$
Ej. 72 mezcla de estereo isó-meros		Ej. 11E		9,82 (Método 2F)	317 $(M+H)^+$
Ej. 73 mezcla racé-mica		Ej. 11E		9,44 (Método 2F)	275 $(M+H)^+$

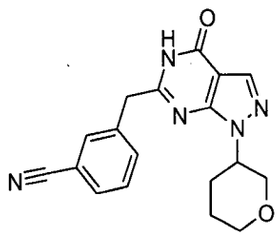
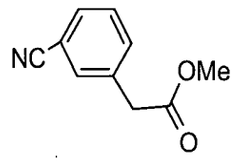
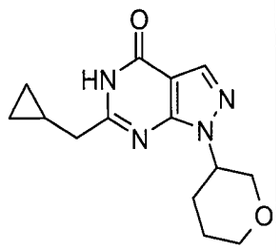
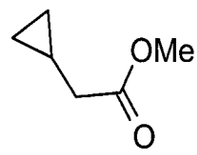
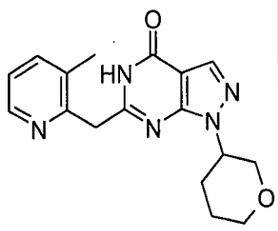
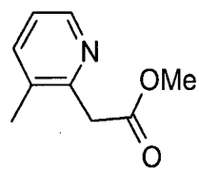
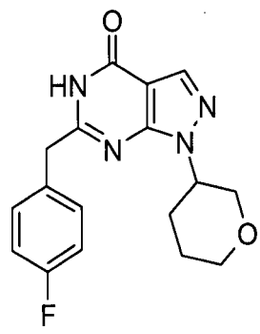
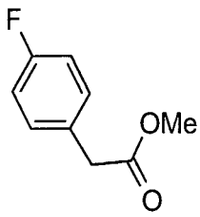
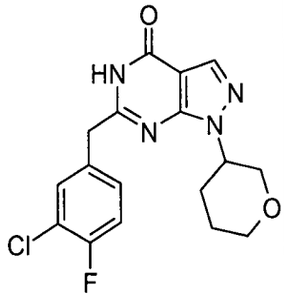
	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 74 mezcla racé-mica		Ej. 11E		8,89 (Método 2F)	263 $(M+H)^+$
Ej. 75 mezcla racé-mica		Ej. 11E		10,69 (Método 2F)	303 $(M+H)^+$
Ej. 76 mezcla racé-mica		Ej. 11E	Ej. 5H	10,57 (Método 2F)	291 $(M+H)^+$
Ej. 77 mezcla de estereo isó-meros		Ej. 11E	Ej. 5T	10,55 (Método 2F)	331 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 78 mezcla racé-mica		Ej. 11E		4,83 (Método 1E hidro)	298 $(M+H)^+$
Ej. 79 mezcla racé-mica		Ej. 11E		7,10 (Método 1E fusión)	315 $(M+H)^+$
Ej. 80 mezcla racé-mica		Ej. 11E		5,97 (Método 1E fusión)	261 $(M+H)^+$
Ej. 81 mezcla de estereo isó-meros		Ej. 11E		4,73 (Método 1E hidro)	291 $(M+H)^+$
Ej. 82 mezcla racé-mica		Ej. 11E	Ej. 5AK	7,37 (Método 1E hidro)	341 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 83 mezcla racé-mica		Ej. 11E	Ej. 5AD	6,85 (Método 1E hidro)	327 $(M+H)^+$
Ej. 84 mezcla de estereo isó-meros		Ej. 11E		6,88 (Método 1E hidro)	277 $(M+H)^+$
Ej. 85 mezcla racé-mica		Ej. 11E	Ej. 5AH	7,93 (Método 1E hidro)	365 $(M+H)^+$
Ej. 86 mezcla racé-mica		Ej. 11E		10,93 (Método 2F)	365 $(M+H)^+$
Ej. 87 mezcla racé-mica		Ej. 11E		5,43 (Método 1E hidro)	312 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 88 mezcla racé-mica		Ej. 11E		5,43 (Método 1E hidro)	312 $(M+H)^+$
Ej. 89 mezcla racé-mica		Ejemplo 11E		5,28 (Método 1E hidro)	322 $(M+H)^+$
Ej. 90 mezcla racé-mica		Ej. 11F	Ej. 5AC	8 (Método 1E hidro)	303 $(M+H)^+$
Ej. 91 mezcla racé-mica		Ej. 11F	Ej. 5AE	8,45 (Método 1E hidro)	395 $(M+H)^+$
Ej. 92 mezcla racé-mica		Ej. 11F		6,93 (Método 1E hidro)	277 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 93 mezcla racé-mica		Ej. 11F	Ej. 5AK	8,20 (Método 1E hidro)	355 $(M+H)^+$
Ej. 94 mezcla racé-mica		Ej. 11F		6,28 (Método 1E hidro)	312 $(M+H)^+$
Ej. 95 mezcla de estereo isó-meros		Ej. 11F		7,70 (Método 1E hidro)	291 $(M+H)^+$
Ej. 96 mezcla racé-mica		Ej. 11F		7,33 (Método 1E hidro)	289 $(M+H)^+$
Ej. 97 mezcla racé-mica		Ej. 11F		8,17 (Método 1E hidro)	379 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 98 mezcla racé-mica		Ej. 11F		6,80 (Método 1E hidro)	336 $(M+H)^+$
Ej. 99 mezcla racé-mica		Ej. 11F		6,43 (Método 1E hidro)	275 $(M+H)^+$
Ej. 100 mezcla racé-mica		Ej. 11F		2,38 (Método 2F)	326 $(M+H)^+$
Ej. 101 mezcla racé-mica		Ej. 11F		7,52 (Método 1E hidro)	329 $(M+H)^+$
Ej. 102 mezcla racé-mica		Ej. 11F	Ej. 5F	8,28 (1E hidro)	363 $(M+H)^+$

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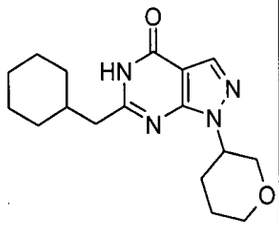
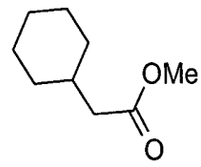
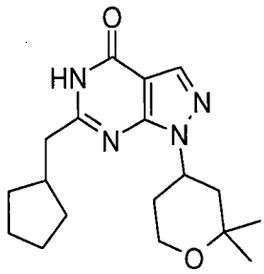
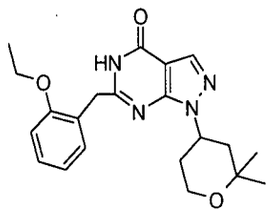
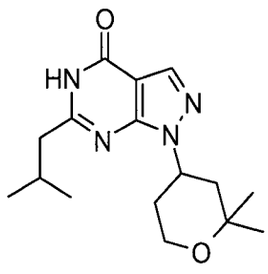
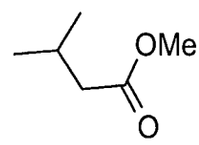
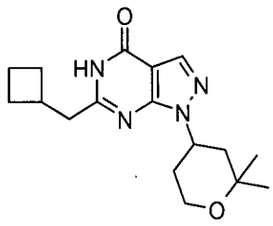
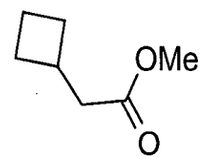
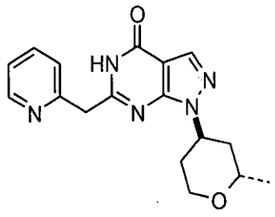
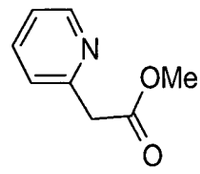
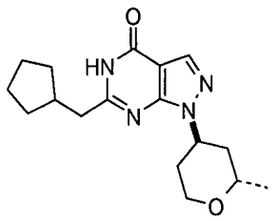
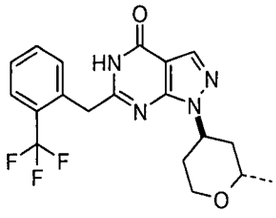
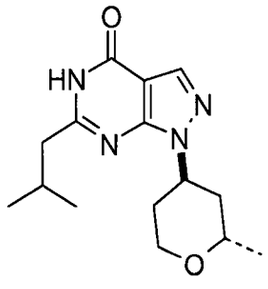
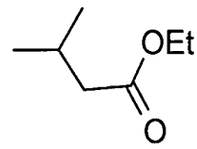
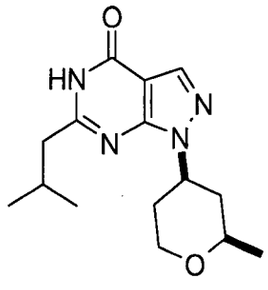
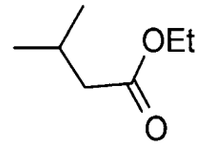
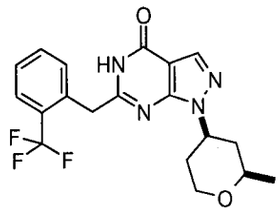
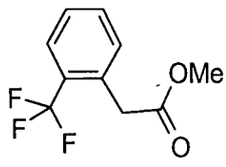
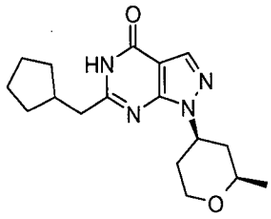
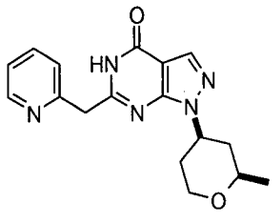
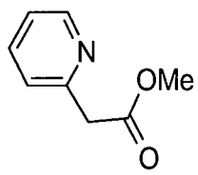
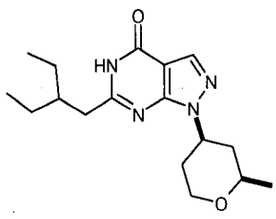
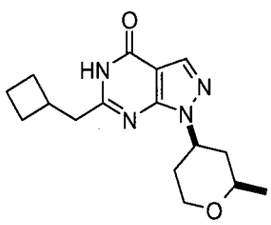
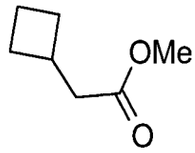
	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 103 mezcla racé-mica		Ej. 11F		8,70 (Método 1E hidro)	317 $(M+H)^+$
Ej. 104 mezcla racé-mica		Ej. 11G	Ej. 5AC	8,57 (Método 1E hidro)	331 $(M+H)^+$
Ej. 105 mezcla racé-mica		Ej. 11G	Ej. 5AK	8,62 (Método 1E hidro)	383 $(M+H)^+$
Ej. 106 mezcla racé-mica		Ej. 11G	Iso-valerato de metilo 	7,58 (Método 1E hidro)	305 $(M+H)^+$
Ej. 108 mezcla racé-mica		Ej. 11G	Éster metílico del ácido ciclo-butil-acético 	7,93 (Método 1E)	317 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 111 mezcla trans; racé-mica		Ej. 11H		2,05 (Método 2F)	326 $(M+H)^+$
Ej. 112 mezcla trans; racé-mica		Ej. 11H	Ej. 5AC	8,25 (Método 2F)	317 $(M+H)^+$
Ej. 113 mezcla trans; racé-mica		Ej. 11H		8,42 (Método 1E hidro)	393 $(M+H)^+$
Ej. 114 mezcla trans; racé-mica		Ej. 11H		7,15 (Método 1E hidro)	291 $(M+H)^+$
Ej. 115 mezcla cis; racé-mica		Ej. 11I		9,90 (Método 2F)	291 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 116 mezcla cis; racé-mica		Ej. 11l		8,18 (Método 1E hidro)	393 $(M+H)^+$
Ej. 117 mezcla cis; racé-mica		Ej. 11l	Ej. 5AC	7,98 (Método 1E hidro)	317 $(M+H)^+$
Ej. 118 mezcla cis; racé-mica		Ej. 11l		5,80 (Método 1E hidro)	326 $(M+H)^+$
Ej. 119 mezcla cis; racé-mica		Ej. 11l	Ej. 5H	8,42 (Método 1E hidro)	319 $(M+H)^+$
Ej. 120 mezcla cis; racé-mica		Ej. 11l		7,33 (Método 1E hidro)	303 $(M+H)^+$

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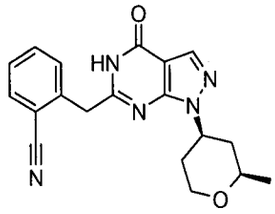
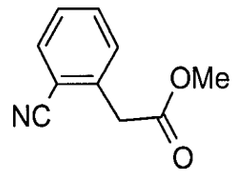
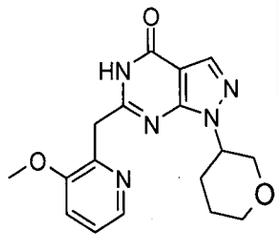
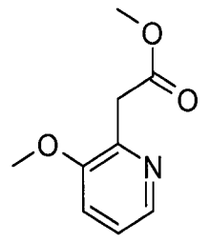
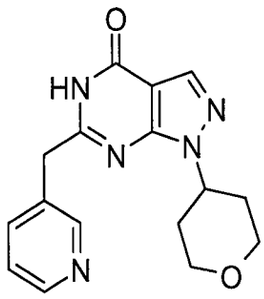
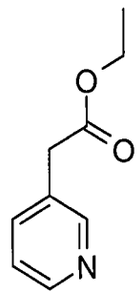
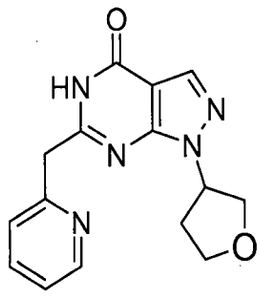
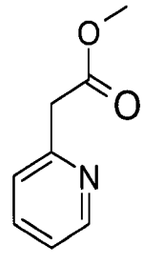
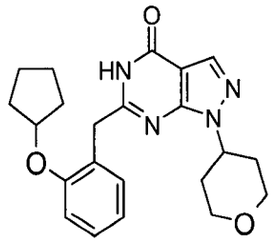
	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 121 mezcla cis; racé-mica		Ej. 11I		9,91 (Método 2F)	350 $(M+H)^+$
Ej. 122 mezcla racé-mica		Ej. 11F		6,95 (Método 2F)	342 (M+H)+
Ej. 123		Ej. 11B		2,12 (Método Grad_C8_ NH_4COOH)	312 $(M+H)^+$
Ej. 124 mezcla racé-mica		Ej. 11E		4,98 (Método 1E hidro)	298 $(M+H)^+$
Ej. 125		Ej. 11B	Ej. 5P	8,72 (Método 1E hidro)	395 $(M+H)^+$

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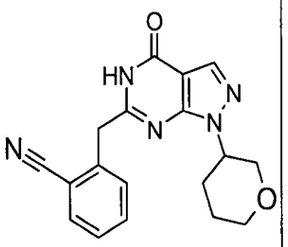
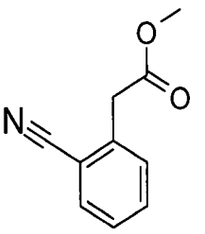
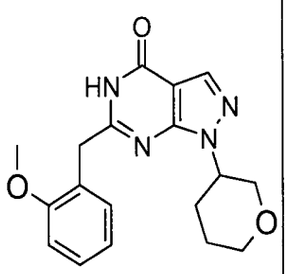
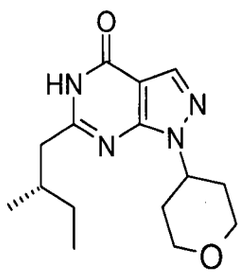
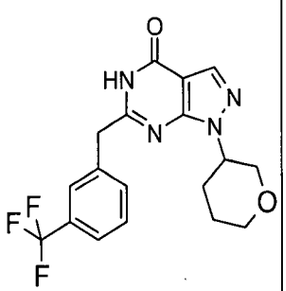
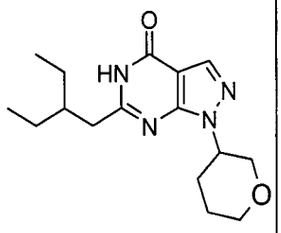
	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 126 mezcla racé-mica		Ej. 11F		9,72 (Método 2F)	336 $(M+H)^+$
Ej. 127 mezcla racé-mica		Ej. 11F	Ej. 5AB	7,62 (Método 1E hidro)	341 $(M+H)^+$
Ej. 128 Enantió mero S		Ej. 11B	Ej. 5G	9,83 (Método 2F)	291 $(M+H)^+$
Ej. 129 mezcla racé-mica		Ej. 11F	Ej. 5AF	11,56 (Método 2F)	379 $(M+H)^+$
Ej. 130 mezcla racé-mica		Ej. 11F	Ej. 5H	8,38 (Método 1E hidro)	305 $(M+H)^+$

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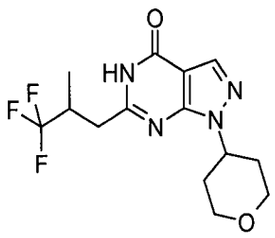
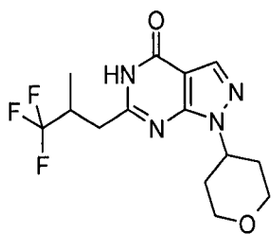
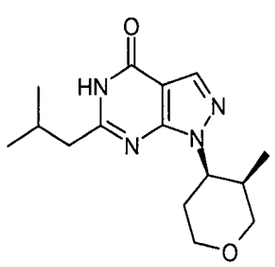
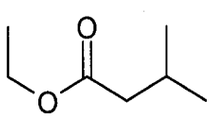
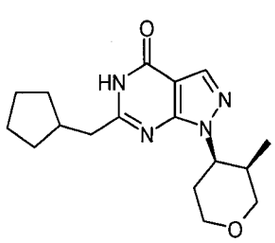
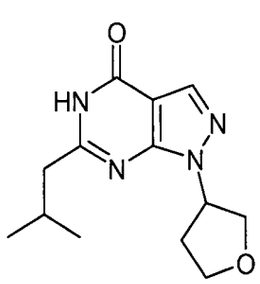
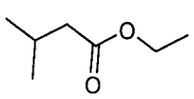
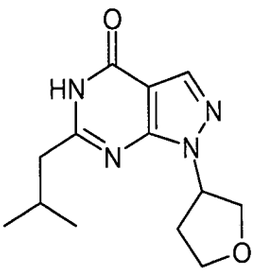
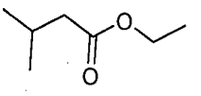
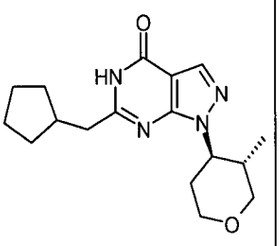
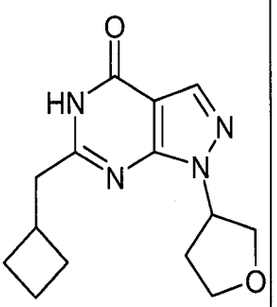
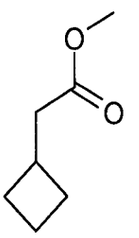
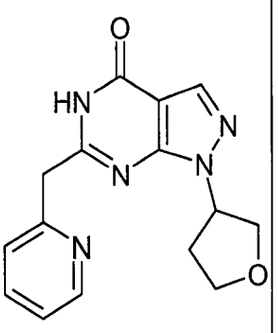
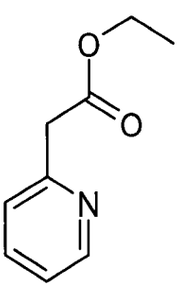
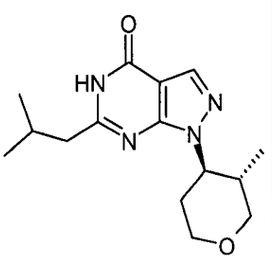
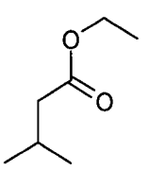
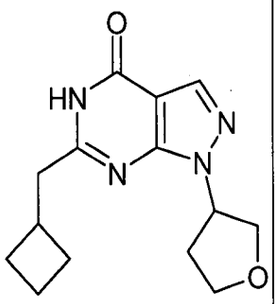
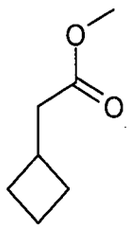
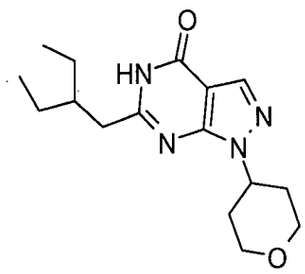
	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 131 Enantiómero A		Ej. 11B	Ej. 5B	9,93 (Método 2F)	331 $(M+H)^+$
Ej. 132 Enantiómero B		Ej. 11B	Ej. 5C	9,93 (Método 2F)	331 $(M+H)^+$
Ej. 132-1 mezcla cis, racémica		Ej. 11IA		9,83 (Método 2F)	291 $(M+H)^+$
Ej. 132-2 mezcla cis, racémica		Ej. 11IA	Ej. 5AC	10,96 (Método 2F)	317 $(M+H)^+$
Ej. 132-3 Enantiómero A		Ej. 15A		8,84 (Método 2F)	263 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
Ej. 132-4 Enantiómero B		Ej. 16A		8,96 (Método 2F)	263 $(M+H)^+$
Ej. 132-5 mezcla trans, racémica		Ej. 11IB	Ej. 5AC	10,21 (Método 2F)	317 $(M+H)^+$
Ej. 132-6 Enantiómero B		Ej. 16A		7,15 (Método 1E hidro)	275 $(M+H)^+$
Ej. 132-7 Enantiómero B		Ej. 16A		5,68 (Método 1E hidro)	298 $(M+H)^+$
Ej. 132-8 mezcla trans, racé-		Ej. 11IB		9,23 (Método 2F)	291 $(M+H)^+$

	Estructura	pirazolil-carboxa-mida	Éster	tiempo de retención [min]	MS (ESI, m/z)
mica					
Ej. 132-9 Enantiómero A		Ej. 15A		8,83 (Método 2L)	275 $(M+H)^+$

Ejemplo 133

6-(2-Etil-butil)-1-(tetrahidro-piran-4-il)-1,5-dihidro-pirazolo[3,4-d]pirimidin-4-ona



Se mezcló el Ejemplo 11B (0,1 g, 0,48 mmol) con ácido polifosfórico (1,0 g) y se añadió ácido 2-(trifluorometoxi)fenilacético (248 mg, 1,9 mmol). Se calentó la mezcla a 120 °C durante 16 horas. Se bajó la temperatura a 20 °C y se ajustó el valor de pH a 7 por adición de amoníaco (solución al 30 % en agua). Se extrajo la fase acuosa con diclorometano (2 x 20 mL) y se secó la fase orgánica sobre sulfato de sodio. Se purificó la mezcla cruda por cromatografía rápida. Eluyente: hexano/acetato de etilo 40/60.

Se obtuvieron 23,5 mg (16 %) como un sólido blanco

HPLC-MS (1E) tiempo de retención: 6,77 min

MS (APCI pos): m/z = 305 (M+H)+

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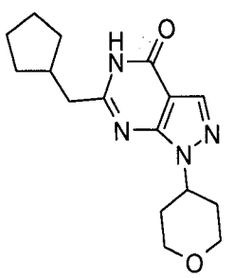
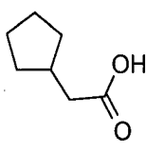
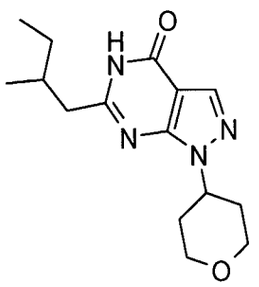
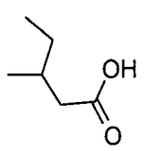
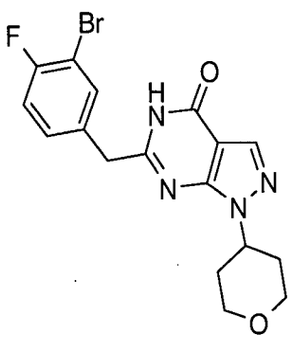
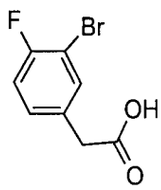
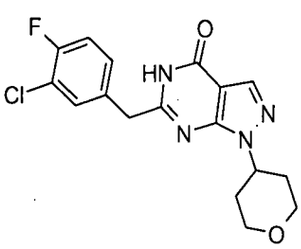
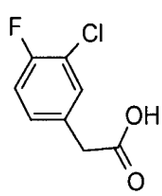
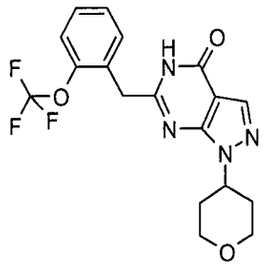
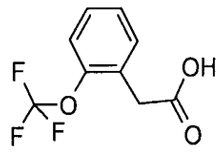
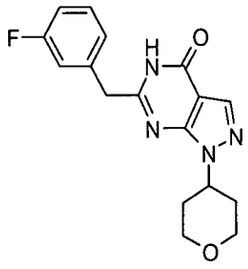
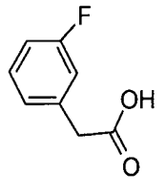
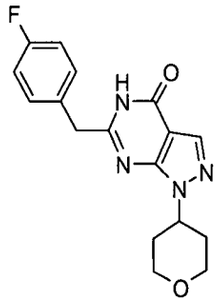
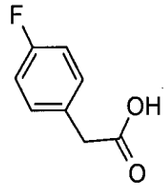
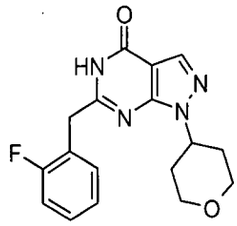
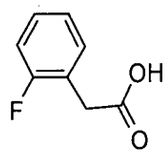
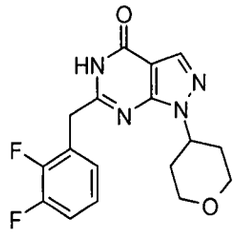
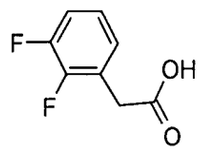
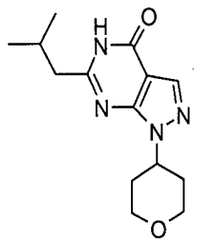
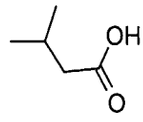
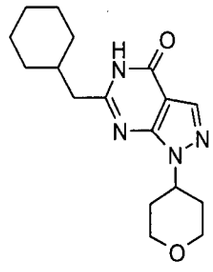
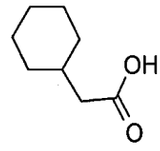
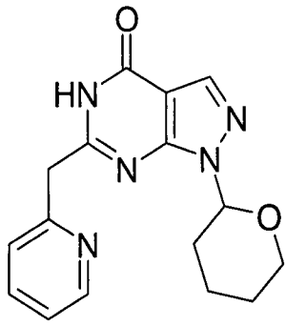
Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 133, utilizando los correspondientes ácidos carboxílicos como materiales de partida:

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ejemplo 134			6,37 (Método 1E)	303 $(M+H)^+$
Ejemplo 135 mezcla racémica			5,95 (Método 1E)	291 $(M+H)^+$
Ejemplo 136			6,57 (Método 1E)	407 $(M+H)^+$
Ejemplo 137			6,48 (Método 1E)	363 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ejemplo 138			6,72 (Método 1E)	395 $(M+H)^+$
Ejemplo 139			2,71 (Método Grad_C8_NH_4COOH)	329 $(M+H)^+$
Ejemplo 140			2,77 (Método Grad_C8_NH_4COOH)	329 $(M+H)^+$
Ejemplo 141			2,90 (Método Grad_C8_NH_4COOH)	329 $(M+H)^+$
Ejemplo 142			3,07 (Método Grad_C8_NH_4COOH)	347 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ejemplo 143			2,71 (Método Grad_C8_NH_4COOH)	277 $(M+H)^+$
Ejemplo 144			3,28 (Método Grad_C8_NH_4COOH)	317 $(M+H)^+$

Ejemplo 145, mezcla racémica

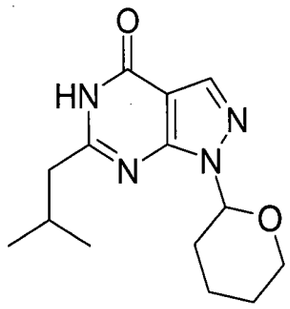
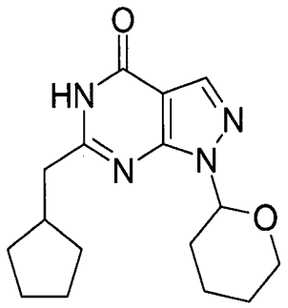
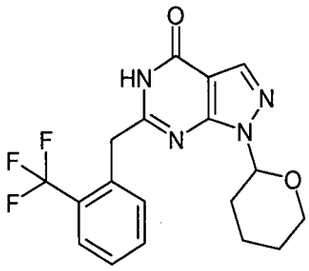


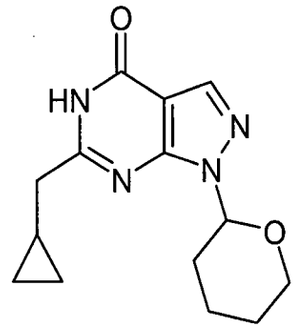
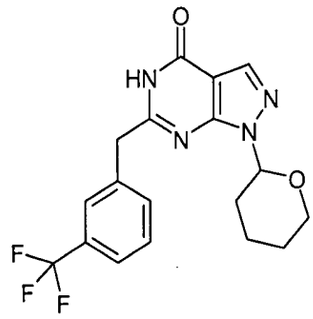
Se mezclaron 106 mg (0,47 mmol) del Ejemplo 12V con 4 mL de acetato de etilo y 0,5 mL de dimetilformamida, se añadieron 51 mg (0,61 mmol) de 3,4-dihidro-2H-pirano y 88,4 mg (0,51 mmol) de ácido p-toluenosulfónico. Se calentó la mezcla de reacción a 60 °C y se agitó durante 2 h. Después de enfriar a temperatura ambiente se añadió acetato de etilo y se lavó la mezcla con hidrogenocarbonato de sodio saturado y con cloruro de sodio saturado. Se evaporó la capa orgánica a presión reducida. Se purificó el residuo por HPLC-MS preparativa. Se obtuvieron 31,5 mg (21,7 %).

MS (APCI pos): m/z = 312 (M+H)+

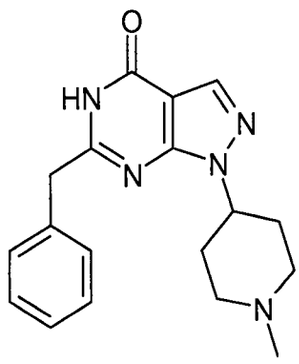
HPLC-MS (Método 2F) tiempo de retención: 8,26 min

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 145, utilizando las correspondientes pirazolopirimidinonas como materiales de partida.

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 146 mezcla racémica		Ejemplo 12W	9,99 (Método 2F)	277 $(M+H)^+$
Ej. 147 mezcla racémica		Ejemplo 12X	10,98 (Método 2F)	303 $(M+H)^+$
Ej. 147-1 mezcla racémica		Ejemplo 12Y	10,98 (Método 2F)	303 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ejemplo 147-2 mezcla racémica		Ejemplo 12AA	9,56 (Método 2F)	275 $(M+H)^+$
Ejemplo 147-3 mezcla racémica		Ejemplo 12Z	11,62 (Método 2F)	379 $(M+H)^+$

Ejemplo 148



Se disolvieron 160 mg (470 mmol) del Ejemplo 12E en 10 mL de metanol y se añadieron 350 mg de níquel Raney. Se hidrogenó la mezcla de reacción a temperatura ambiente durante 6 h, se filtró y se evaporó el disolvente a presión reducida. Se obtuvieron 100 mg (65 %) del producto.

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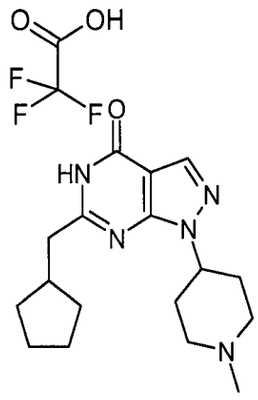
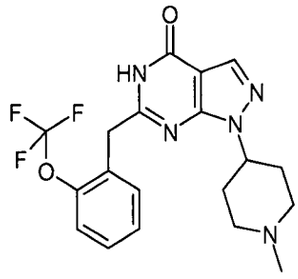
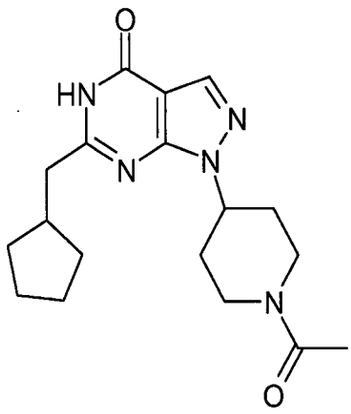
HPLC-MS (Método 1): tiempo de retención: 0,95 min

MS (ESI pos): m/z = 324 (M+H)

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 148, utilizando los correspondientes N-óxidos como materiales de partida.

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 149		Ejemplo 12D	0,95 (Método 1)	316 $(M+H)^+$
Ej. 150		Ejemplo 12F	1,11 (Método 1)	408 $(M+H)^+$

Ejemplo 151

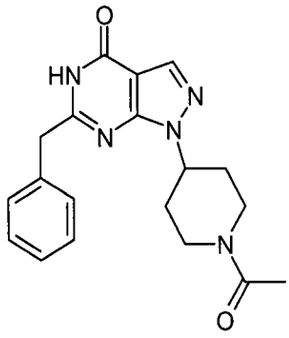
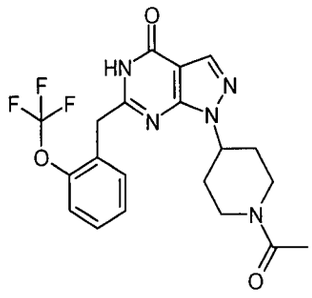
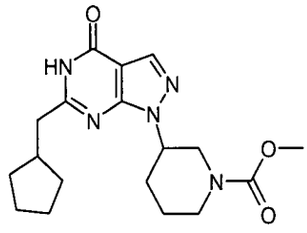
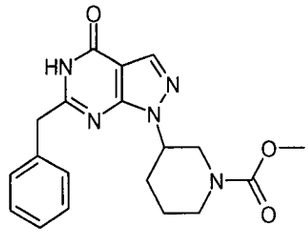
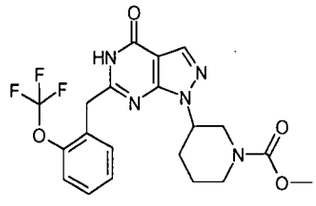
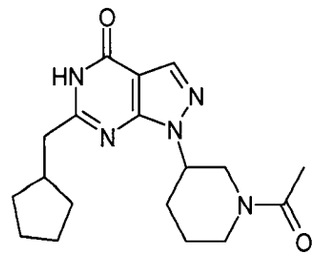


Se disolvieron 62 mg (150 mmol) del Ejemplo 13B en 4 mL de diclorometano, se añadieron 22,5 µL (300 mmol) de cloruro de acetilo y 42 µL (300 mmol) de trietilamina. Se agitó la mezcla de reacción a temperatura ambiente durante la noche. Se separó el disolvente a presión reducida. Se purificó el residuo por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 28 mg (55 %) del producto.

HPLC-MS (Método 1): tiempo de retención: 1,18 min

MS (ESI pos): m/z = 344 (M+H)+

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 151, utilizando los correspondientes materiales de partida. Será evidente que cuando no se ha introducido cloruro de acetilo como agente acilante para todos los compuestos, se utilizaron otros agentes acilantes como metoxicloroformiato, cloruro de aminocarbonilo sustituido o insustituido, cloruro de fenoxicarbonilo sustituido o insustituido, cloruro de benzoilo sustituido o insustituido, comercialmente disponibles.

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 152		Ejemplo 13K	1,09 (Método 1)	352 $(M+H)^+$
Ej. 153		Ejemplo 13L	1,25 (Método 1)	436 $(M+H)^+$
Ej. 154 mezcla racémica		Ejemplo 13C	1,38 (Método 1)	360 $(M+H)^+$
Ej. 155 mezcla racémica		Ejemplo 13D	1,30 (Método 1)	368 $(M+H)^+$
Ej. 156 mezcla racémica		Ejemplo 13E	1,44 (Método 1)	452 $(M+H)^+$
Ej. 157 mezcla racémica		Ejemplo 13C	1,20 (Método 1)	344 $(M+H)^+$

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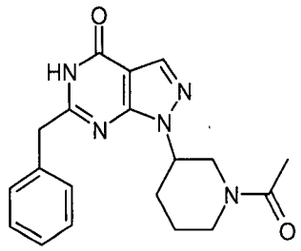
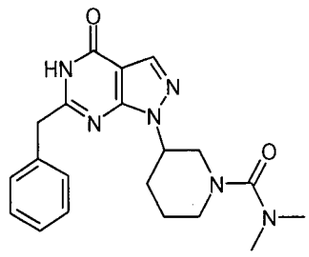
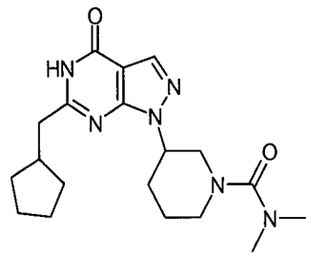
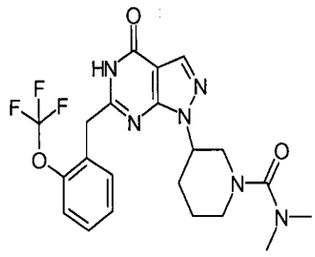
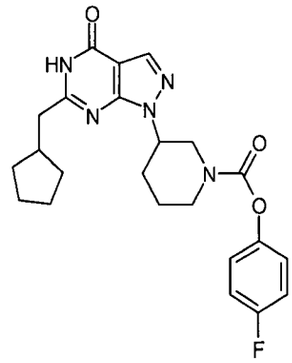
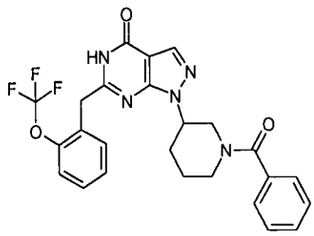
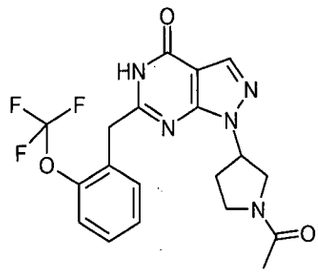
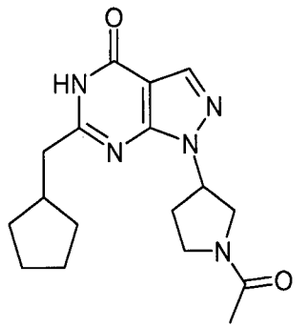
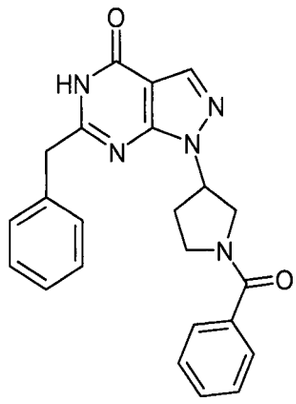
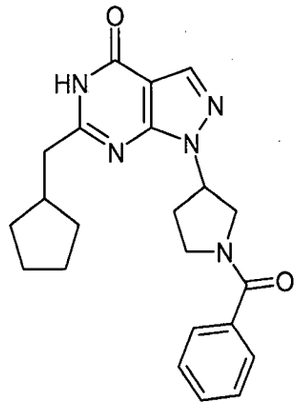
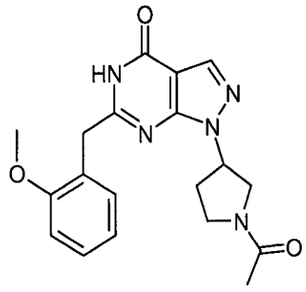
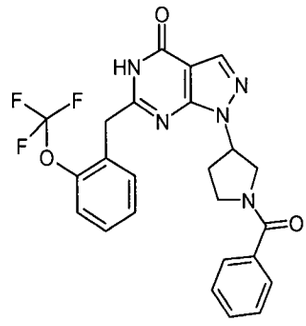
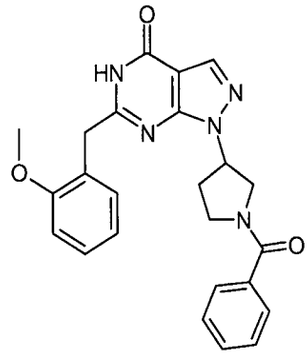
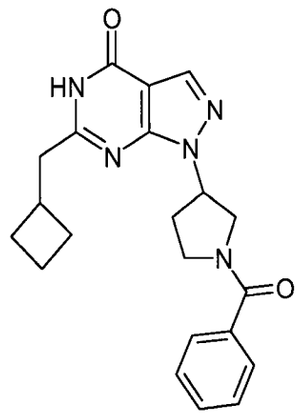
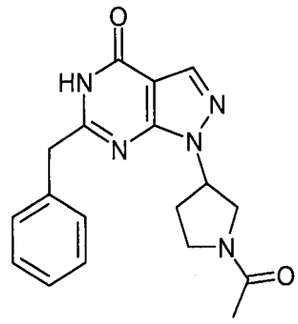
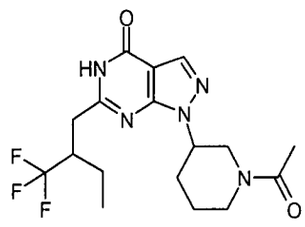
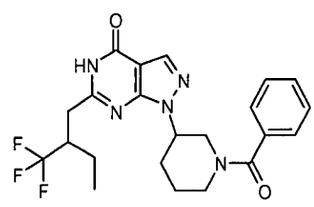
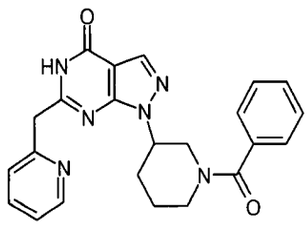
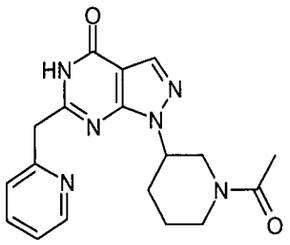
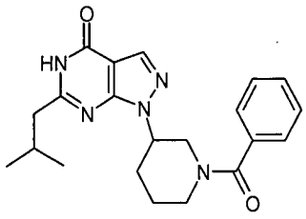
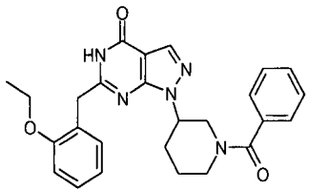
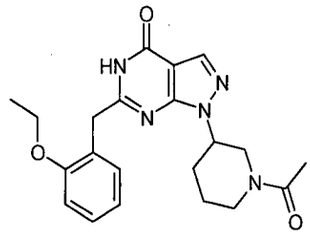
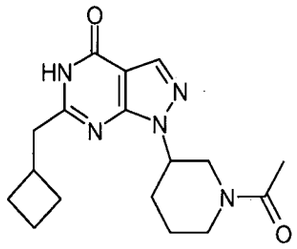
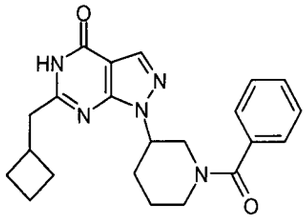
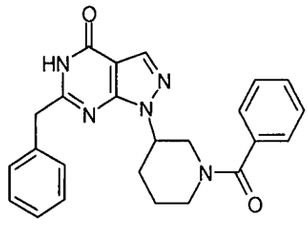
	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 158 mezcla racémica		Ejemplo 13D	1,16 (Método 1)	352 $(M+H)^+$
Ej. 159 mezcla racémica		Ejemplo 13D	1,25 (Método 1)	381 $(M+H)^+$
Ej. 160 mezcla racémica		Ejemplo 13C	1,30 (Método 1)	373 $(M+H)^+$
Ej. 161 mezcla racémica		Ejemplo 13E	1,38 (Método 1)	465 $(M+H)^+$
Ej. 162 mezcla racémica		Ejemplo 13C	1,62 (Método 1)	440 $(M+H)^+$

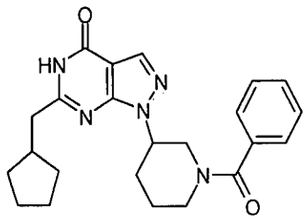
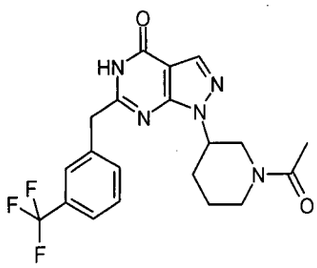
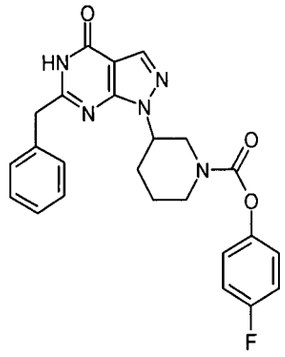
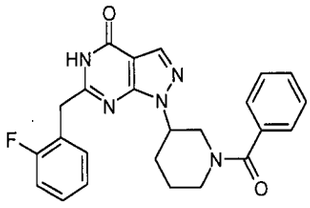
	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 163 mezcla racémica		Ejemplo 13E	1,48 (Método 1)	498 $(M+H)^+$
Ej. 164 mezcla racémica		Ejemplo 13G	1,23 (Método 1)	422 $(M+H)^+$
Ej. 165 mezcla racémica		Ejemplo 13A	1,14 (Método 1)	330 $(M+H)^+$
Ej. 166 mezcla racémica		Ejemplo 13F	1,28 (Método 1)	400 $(M+H)^+$

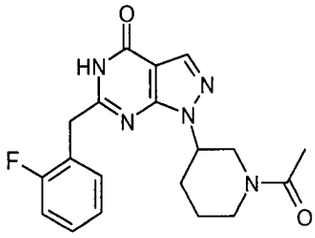
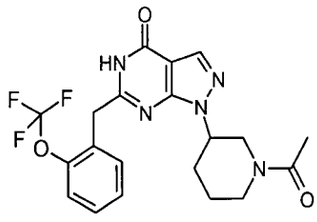
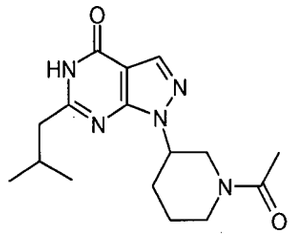
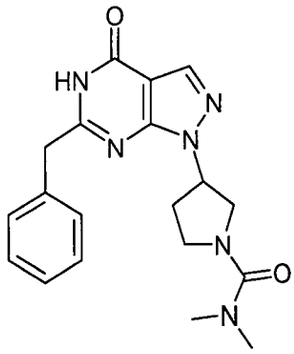
	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 167 mezcla racémica		Ejemplo 13A	1,36 (Método 1)	392 $(M+H)^+$
Ej. 168 mezcla racémica		Ejemplo 13H	1,1 (Método 1)	368 $(M+H)^+$
Ej. 169 mezcla racémica		Ejemplo 13G	1,44 (Método 1)	484 $(M+H)^+$
Ej. 170 mezcla racémica		Ejemplo 13H	1,32 (Método 1)	430 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 171 mezcla racémica		Ejemplo 13I	1,29 (Método 1)	378 $(M+H)^+$
Ej. 172 mezcla racémica		Ejemplo 13F	1,07 (Método 1)	338 $(M+H)^+$
Ej. 173 mezcla de estereoisómeros		Ejemplo 13M	1,25 (Método 1)	386 $(M+H)^+$
Ej. 174 mezcla de estereoisómeros		Ejemplo 13M	1,44 (Método 1)	448 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 175 mezcla racémica		Ejemplo 13N	1,04 (Método 1)	415 $(M+H)^+$
Ej. 176 mezcla racémica		Ejemplo 13N	0,84 (Método 1)	353 $(M+H)^+$
Ej. 177 mezcla racémica		Ejemplo 13O	1,31 (Método 1)	380 $(M+H)^+$
Ej. 178 mezcla racémica		Ejemplo 13P	1,43 (Método 1)	458 $(M+H)^+$

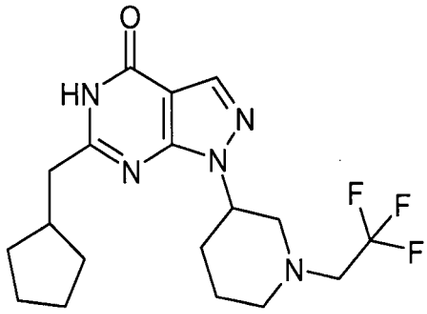
	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 179 mezcla racémica		Ejemplo 13P	1,24 (Método 1)	396 $(M+H)^+$
Ej. 180 mezcla racémica		Ejemplo 13Q	1,14 (Método 1)	330 $(M+H)^+$
Ej. 181 mezcla racémica		Ejemplo 13Q	1,34 (Método 1)	392 $(M+H)^+$
Ej. 182 mezcla racémica		Ejemplo 13D	1,35 (Método 1)	414 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 183 mezcla racémica		Ejemplo 13C	1,41 (Método 1)	406 $(M+H)^+$
Ej. 184 mezcla racémica		Ejemplo 205	1,30 (Método 1)	420 $(M+H)^+$
Ej. 185 mezcla racémica		Ejemplo 13D	1,53 (Método 1)	448 $(M+H)^+$
Ej. 186 mezcla racémica		Ejemplo 204	1,35 (Método 1)	432 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 187 mezcla racémica		Ejemplo 204	1,15 (Método 1)	370 $(M+H)^+$
Ej. 188 mezcla racémica		Ejemplo 13E	1,29 (Método 1)	436 $(M+H)^+$
Ej. 189 mezcla racémica		Ejemplo 13O	1,08 (Método 1)	318 $(M+H)^+$
Ej. 190 mezcla racémica		Ejemplo 13F	1,18 (Método 1)	367 $(M+H)^+$

Ejemplo 191, mezcla racémica

632

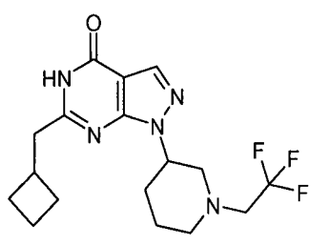


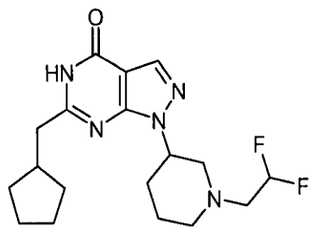
Se disolvieron 60 mg (0,2 mmol) del Ejemplo 13C en 5 mL de xileno y se añadieron gota a gota 57 mg (0,2 mmol) de 2,2,2-trifluoroetil-triclorometanosulfonato. Se calentó la mezcla de reacción a 140 °C y se agitó durante 5 h. Se separó el disolvente a presión reducida. Se purificó el residuo por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 24,8 mg (32 %) del producto.

HPLC-MS (Método 1): tiempo de retención: 1,45 min

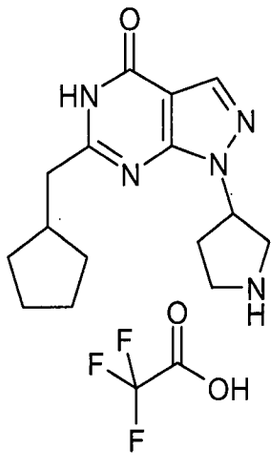
MS (ESI pos): m/z = 384 $(M+H)^+$

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 191, utilizando los correspondientes materiales de partida.

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 192 mezcla racémica		Ejemplo 13Q	1,35 (Método 1)	370 $(M+H)^+$

Ej. 193 mezcla racémica		Ejemplo 13C	1,07 (Método 1)	366 $(M+H)^+$

Ejemplo 194, mezcla racémica

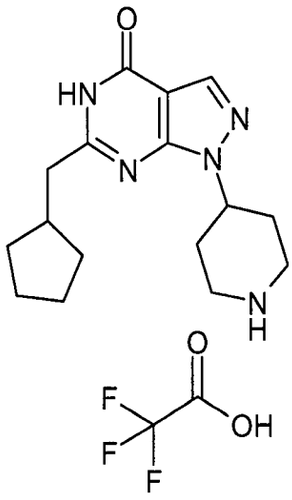


Se disolvieron 400 mg (1,35 mmol) del Ejemplo 11A en 8 mL de etanol absoluto, se añadieron 840 mg (5,4 mmol) del Ejemplo 5AC y 220 mg (5,5 mmol) de hidruro de sodio (suspensión al 60 % en aceite mineral). Se calentó la mezcla de reacción a 150 °C durante 30 min en un horno de microondas. Después de enfriar a temperatura ambiente se acidificó la mezcla de reacción con ácido clorhídrico 4 N. Se separó el disolvente a presión reducida. Se purificó el residuo por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 250 mg (46 %) del producto como un sólido blanco.

HPLC-MS (Método 1): tiempo de retención: 0,93 min

MS (ESI pos): m/z = 288 (M+H)+

Ejemplo 195



Se disolvieron 330 mg (0,82 mmol) del Ejemplo 12A en 3 mL de diclorometano y se añadió 1 mL de ácido trifluoroacético. Se agitó la mezcla de reacción a temperatura ambiente durante la noche. Se evaporó el disolvente a presión reducida. Se purificó el residuo por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 240 mg (70 %) del producto.

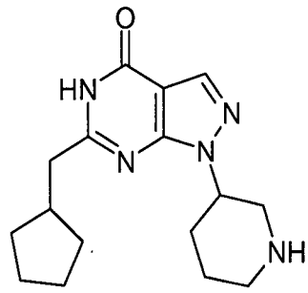
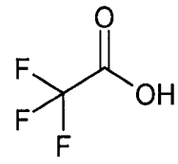
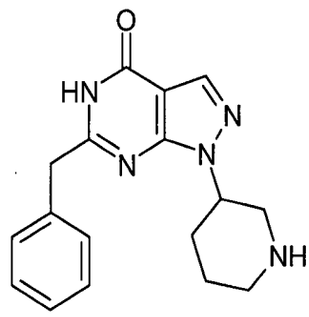
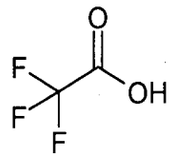
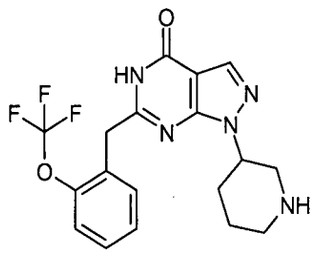
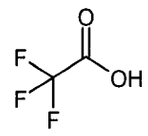
HPLC-MS (Método 1): tiempo de retención: 0,96 min

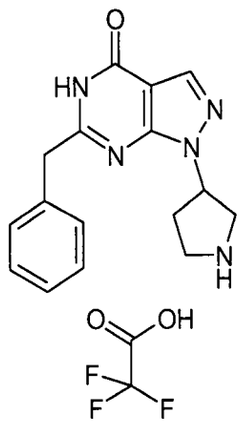
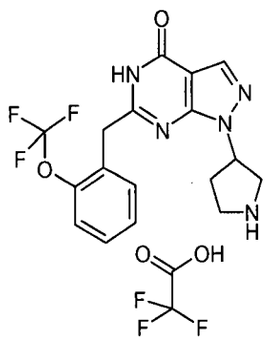
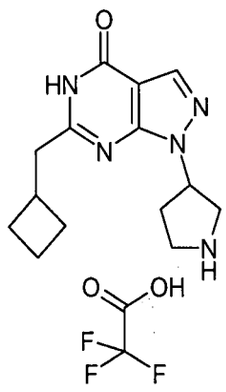
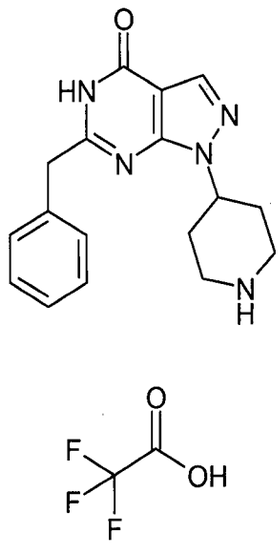
MS (ESI pos): m/z = 302 (M+H)+

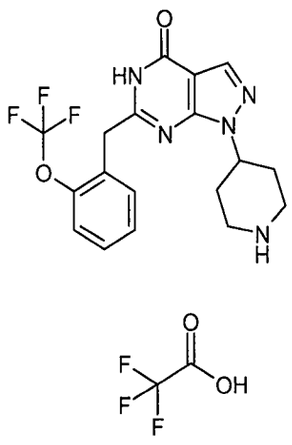
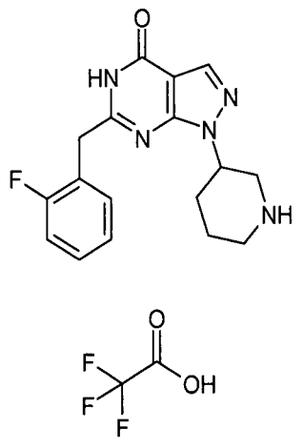
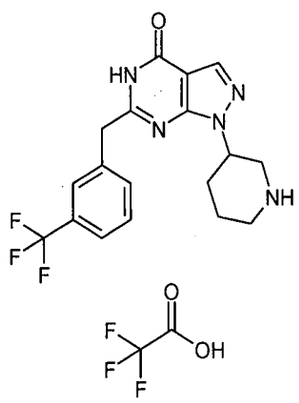
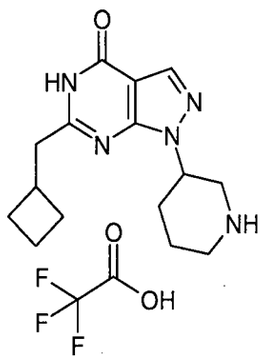
Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 195, utilizando las correspondientes aminas protegidas con Boc como materiales de partida

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)

635

Ej. 196 mezcla racémica	 	Ejemplo 12L	1,01 (Método 1)	302 $(M+H)^+$
Ej. 197 mezcla racémica	 	Ejemplo 12M	0,93 (Método 1)	310 $(M+H)^+$
Ej. 198 mezcla racémica	 	Ejemplo 12N	1,09 (Método 1)	394 $(M+H)^+$

Ej. 199 mezcla racémica		Ejemplo 12G	0,92 (Método 1)	296 $(M+H)^+$
Ej. 200 mezcla racémica		Ejemplo 12H	1,08 (Método 1)	380 $(M+H)^+$
Ej. 201 mezcla racémica		Ejemplo 12J	0,89 (Método 1)	274 $(M+H)^+$
Ej. 202		Ejemplo 12B	0,92 (Método 1)	310 $(M+H)^+$

Ej. 203		Ejemplo 12C	1,07 (Método 1)	394 $(M+H)^+$
Ej. 204 mezcla racémica		Ejemplo 12Q	0,95 (Método 1)	328 $(M+H)^+$
Ej. 205 mezcla racémica		Ejemplo 12R	1,13 (Método 1)	378 $(M+H)^+$
Ej. 206 mezcla racémica		Ejemplo 12U	0,94 (Método 1)	288 $(M+H)^+$

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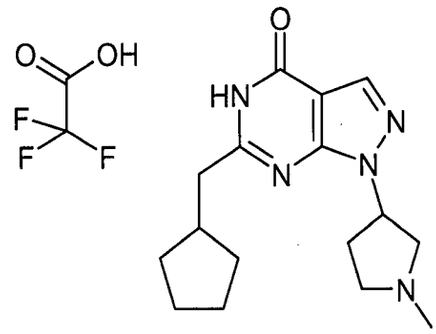
Ejemplo 207, mezcla racémica



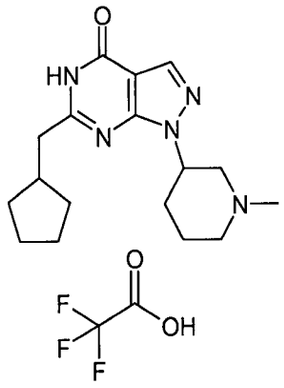
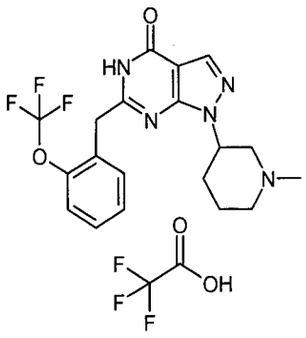
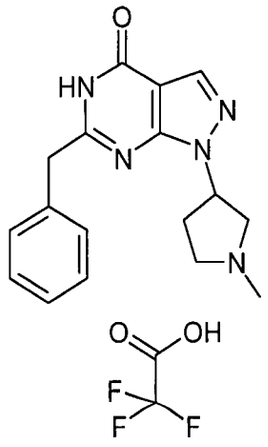
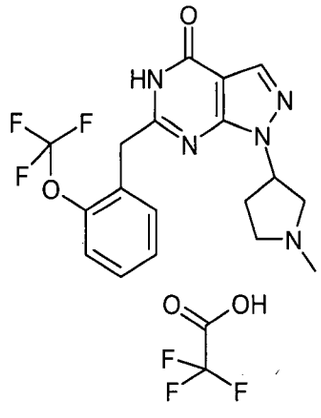
Se disolvieron 50 mg (120 mmol) del Ejemplo 13A en 5 mL de diclorometano y se añadieron 15 mg (500 mmol) de formaldehído. Se agitó la mezcla de reacción a temperatura ambiente durante 1 h. Se añadieron 15 µL (260 mmol) de ácido acético y 35 mg (160 mmol) de triacetoxiborohidruro de sodio. Se agitó la mezcla de reacción durante 2 h a temperatura ambiente. Se separó el disolvente a presión reducida. Se purificó el residuo por HPLC preparativa (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo). Se obtuvieron 34 mg (65 %) del producto.

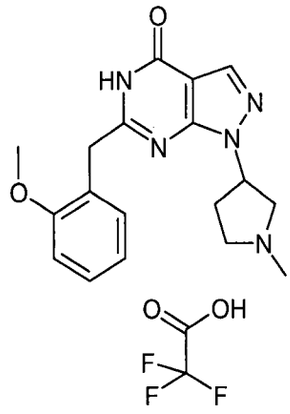
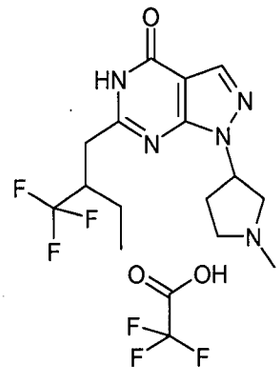
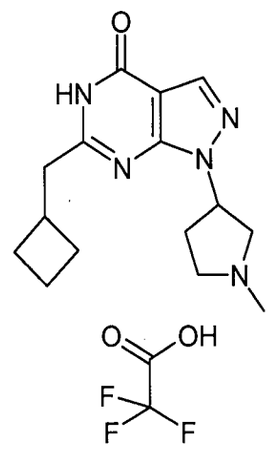
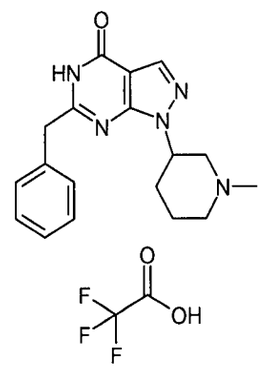
HPLC-MS (Método 1): tiempo de retención: 0,99 min

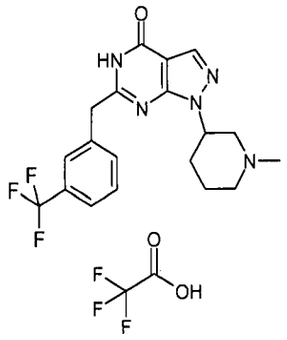
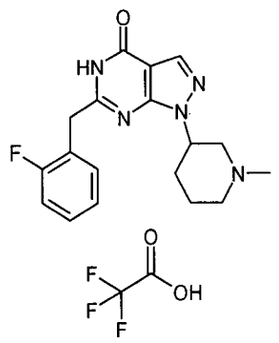
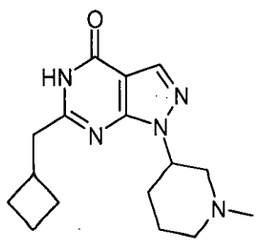
MS (ESI pos): m/z = 302 (M+H)+

Los siguientes ejemplos se sintetizaron de manera análoga a la preparación del Ejemplo 207 utilizando las correspondientes aminas como materiales de partida

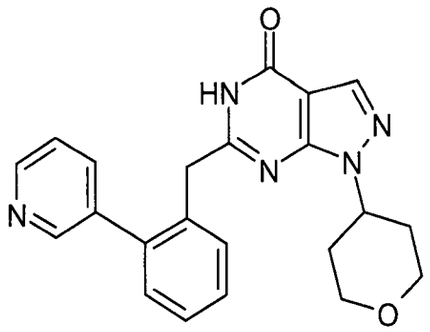
	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 208 mezcla racémica		Ejemplo 13C	1,02 (Método 1)	316 $(M+H)^+$
Ej. 209 mezcla racémica		Ejemplo 13E	1,13 (Método 1)	408 $(M+H)^+$
Ej. 210 mezcla racémica		Ejemplo 13F	0,93 (Método 1)	310 $(M+H)^+$
Ej. 211 mezcla racémica		Ejemplo 13G	1,11 (Método 1)	394 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 212 mezcla racémica		Ejemplo 13H	0,98 (Método 1)	340 $(M+H)^+$
Ej. 213 mezcla de estereoisómeros		Ejemplo 13J	1,02 (Método 1)	344 $(M+H)^+$
Ej. 214 mezcla racémica		Ejemplo 13I	0,91 (Método 1)	288 $(M+H)^+$
Ej. 215 mezcla racémica		Ejemplo 13D	0,97 (Método 1)	324 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ej. 216 mezcla racémica		Ejemplo 205	1,16 (Método 1)	392 $(M+H)^+$
Ej. 217 mezcla racémica		Ejemplo 204	0,98 (Método 1)	342 $(M+H)^+$
Ej. 218 mezcla racémica		Ejemplo 13Q	0,95 (Método 1)	302 $(M+H)^+$

Ejemplo 219



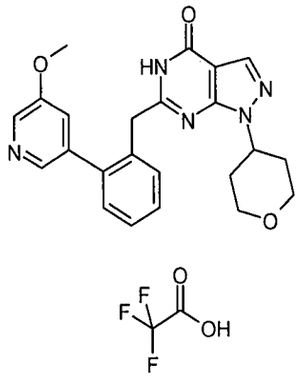
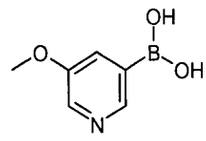
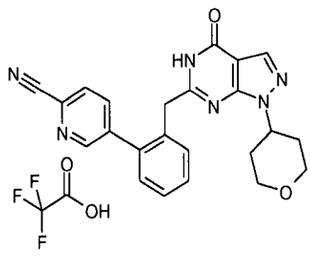
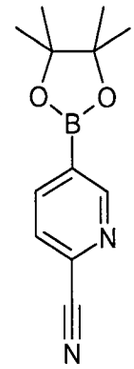
Bajo una atmósfera de argón, se combinaron 100 mg (0,26 mmol) del ejemplo 5, 95 mg (0,77 mmol) de ácido piridin-3-borónico, 310 µL (2,41 mmol) de solución acuosa

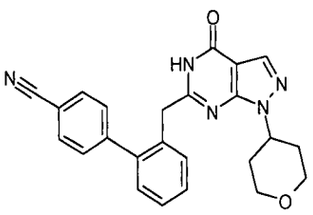
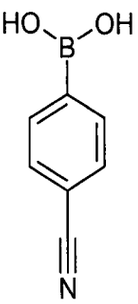
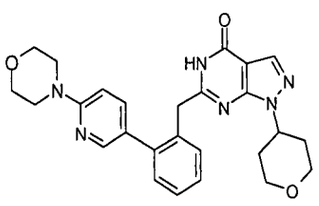
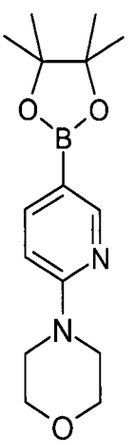
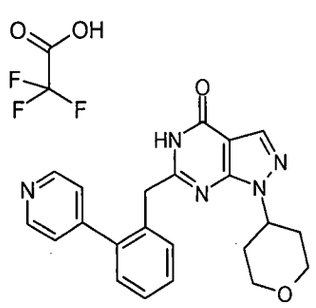
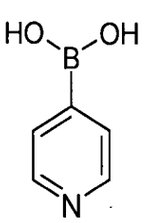
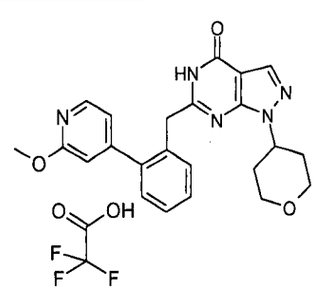
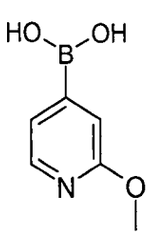
de carbonato de sodio (2 M), 5 mL de dioxano y 20 mg (0,02 mmol) de tetrakis-(trifenilfosfina)paladio(0). Se calentó la mezcla de reacción a 140 °C durante 35 min en un horno de microondas. Después de enfriar a temperatura ambiente se filtró la mezcla de reacción sobre celita. Se evaporó el filtrado a presión reducida. Se purificó el residuo por HPLC preparativa. Se obtuvieron 82 mg (83 %) del producto.

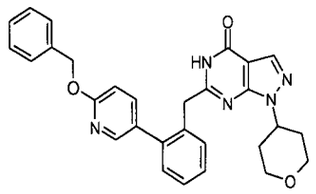
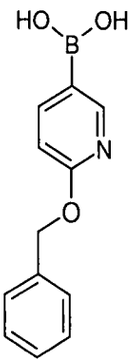
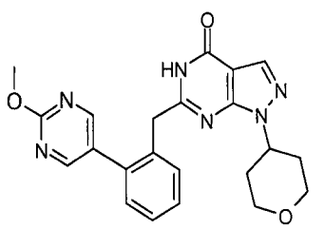
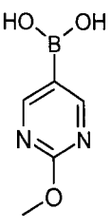
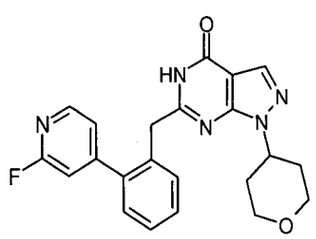
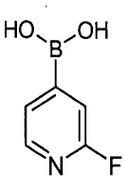
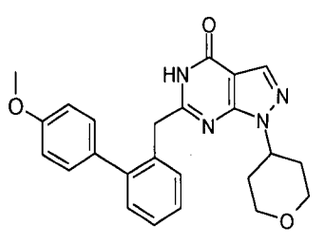
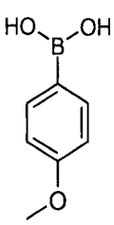
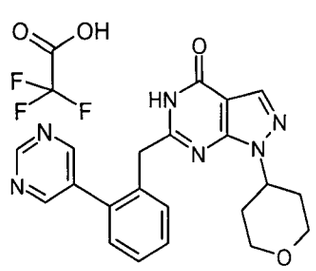
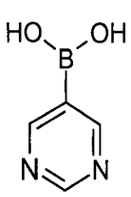
HPLC-MS (Método 1): tiempo de retención: 1,00 min

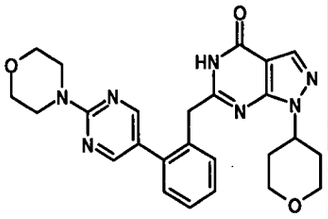
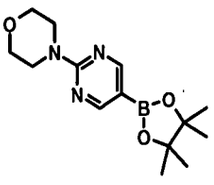
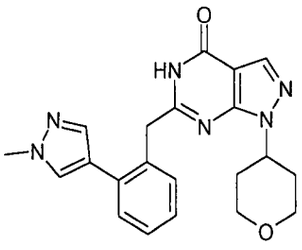
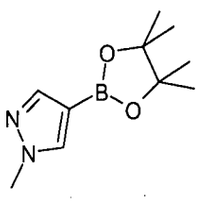
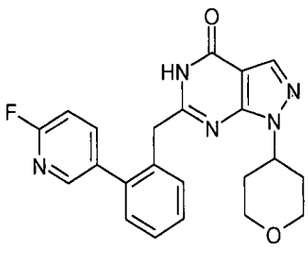
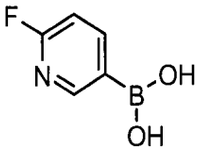
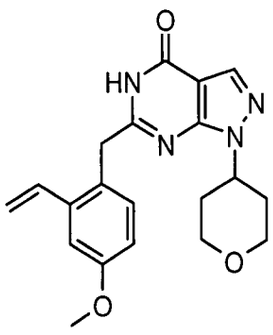
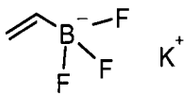
MS (ESI pos): m/z = 388 (M+H)+

Los siguientes ejemplos fueron sintetizados análogamente a la preparación del Ejemplo 219, utilizando los correspondientes ácidos borónicos como materiales de partida:

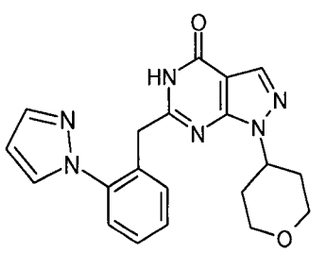
	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ejemplo 220			1,01 (Método 1)	418 $(M+H)^+$
Ejemplo 221			1,24 (Método 1)	413 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ejemplo 222			1,34 (Método 1)	412 $(M+H)^+$
Ejemplo 223			1,03 (Método 1)	473 $(M+H)^+$
Ejemplo 224			0,96 (Método 1)	388 $(M+H)^+$
Ejemplo 225			1,18 (Método 1)	418 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ejemplo 226			1,57 (Método 1)	494 $(M+H)^+$
Ejemplo 227			1,19 (Método 1)	419 $(M+H)^+$
Ejemplo 228			1,26 (Método 1)	406 $(M+H)^+$
Ejemplo 229			1,40 (Método 1)	417 $(M+H)^+$
Ejemplo 230			1,06 (Método 1)	389 $(M+H)^+$

	estructura	material de partida	tiempo de retención [min]	MS (ESI, m/z)
Ejemplo 230-1			1,24 (Método 1)	474 $(M+H)^+$
Ejemplo 230-2			1,16 (Método 1)	391 $(M+H)^+$
Ejemplo 230-3			1,25 (Método 1)	404 $(M+H)^+$
230-4			1,28 (Método 1)	367 $(M+H)^+$

Ejemplo 231

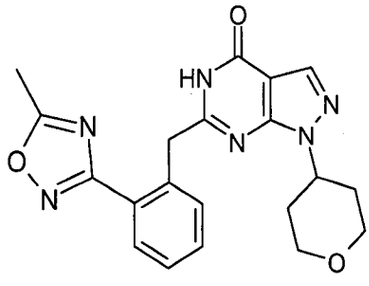


Se cargó un vial bajo atmósfera inerte con el Ejemplo 5 (175 mg, 0,45 mmol), y se añadieron pirazol (306 mg, 4,49 mmol), yoduro de cobre (85 mg, 0,45 mmol) y carbonato de cesio (439 mg, 1,35 mmol). Se añadió entonces dimetilformamida (5 mL), previamente desgasificada, seguida por N-N'-dimetiletilendiamina (47,87 µL; 0,45 mmol). Se calentó la mezcla de reacción a 120 °C durante tres horas. Se filtró entonces la suspensión sobre un lecho de Celita; se lavó la Celita con DMF. Se redujo el volumen de la fase orgánica a presión reducida y, después, se añadió solución saturada de cloruro de amonio, seguida por acetato de etilo. Se separaron las fases y la fase orgánica se lavó con salmuera y después se secó. El producto crudo se purificó en un cartucho SPE y el producto obtenido se purificó adicionalmente por SPE Stratosphere "PL-THIOL MP" para separar completamente las sales de cobre. El sólido obtenido se trituró con éter dietílico. Se obtuvieron 15,5 mg del compuesto deseado (rendimiento = 9,2 %).

HPLC-MS (Método 1E hidro): tiempo de retención: 7,80 min

MS (ESI pos): m/z = 377 (M+H)+

Ejemplo 232



Se mezclaron el Ejemplo 53 (100 mg, 0,298 mmol) e hidroxilamina (0,073 mL, 1,19 mmol) en etanol absoluto (4 mL) en un matraz de 50 mL. Se mantuvo a reflujo la mezcla de reacción durante 3 horas antes del tratamiento. Se separó entonces el disolvente a presión reducida para obtener 120 mg (70 % de contenido, 0,228 mmol) de N-hidroxi-2-[4-oxo-1-(tetrahidro-piran-4-il)-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-ilmetil]-benzamidina como un sólido que se utilizó tal cual en la siguiente etapa.

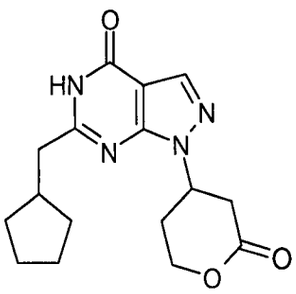
Se suspendió la N-hidroxi-2-[4-oxo-1-(tetrahidro-piran-4-il)-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-ilmetil]-benzamidins (120 mg, 70 % de contenido; 0,228 mmol) en ortoacetato de trimetilo (5 mL) y después se añadió ácido acético (1 mL);

se calentó la mezcla a 100 °C durante una hora. Se enfrió la mezcla a temperatura ambiente y se observó la precipitación de un sólido. Se evaporó el filtrado a presión reducida; el producto crudo se purificó por cromatografía rápida. Se trituró entonces el producto con éter dietílico. Se obtuvieron 24 mg del compuesto deseado (rendimiento 26,6 %).

HPLC/MS (Método 1E hidro)

MS (ESI pos): m/z = 393 (M+H)+

Ejemplo 233



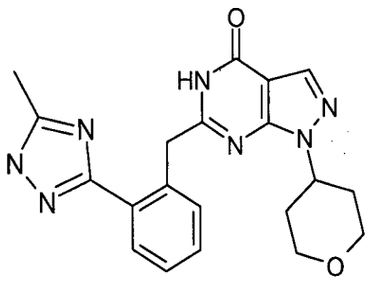
Se disolvió el Ejemplo 12X (250 mg, 1,14 mmol) en 20 mL de metanol caliente. Se añadió alúmina (neutra) y se separó entonces el disolvente para dar un polvo blanco que se transfirió a un vial Wheaton de 2 mL; se añadió 5,6-dihidro-2H-piran-2-oxo seguido por DMFe (1 mL) y se cerró el vial herméticamente. Se calentó la suspensión a 80 °C con agitación orbital durante 4 días. Se filtró entonces la reacción y se lavó la alúmina con metanol, acetato de etilo y diclorometano; se reunieron las soluciones orgánicas y se separaron los disolventes a presión reducida. El producto crudo se purificó por cromatografía rápida.

Eluyente: (gradiente empezando con *n*-hexano/acetato de etilo 9/1 hasta acetato de etilo (100 %) seguido por acetato de etilo/metanol 99/1 hasta 94/6). Se obtuvieron 70 mg del compuesto deseado como un sólido (19,3 %).

HPLC-MS (Método 2F): tiempo de retención: 9,06 min

MS (ESI pos): m/z = 317 (M+H)+

Ejemplo 234

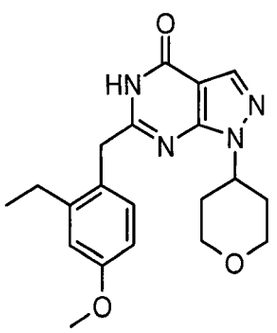


Se mezclaron el Ejemplo 53 (160 mg, 80 % de contenido, 0,38 mmol) e hidrato de hidrazina (0,186 mL, 3,81 mmol) en etanol absoluto (4 mL) en un matraz de 25 mL. Se mantuvo a reflujo la mezcla de reacción durante 6 horas antes del tratamiento. Se separó el disolvente a presión reducida para obtener 200 mg (70 % de contenido, 0,38 mmol) del material deseado utilizado tal cual en la siguiente etapa. Se suspendió el material (200 mg, 70 % de contenido, 0,38 mmol) en ortoacetato de trimetilo (6 mL). Se añadió ácido acético (0,6 mL) y se calentó la solución a 80 °C durante 30 minutos. Se separaron el ortoacetato de trimetilo y el ácido acético a presión reducida y el producto crudo se sometió a reparto entre agua y diclorometano. Se secó la fase orgánica y el producto crudo se purificó por cromatografía rápida. (gradiente: empezando con diclorometano/metanol 98/2 y acabando con diclorometano/metanol 90/10). Se purificó adicionalmente el producto por trituración con éter dietílico. Se obtuvieron 8 mg del compuesto deseado (4 %).

HPLC-MS (Método 1E hidro): tiempo de retención: 6,82 min

MS (ESI pos): m/z = 392 (M+H)+

Ejemplo 235



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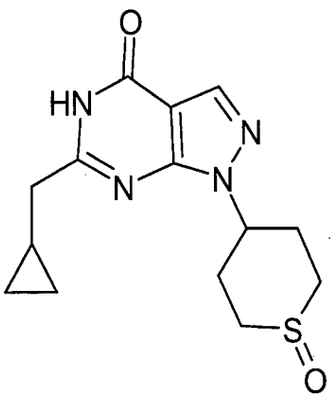
Se hidrogenaron 22 mg (0,06 mmol) del ejemplo 230-4 en 3 mL de metanol, sobre Pd/C (al 10 %) a presión atmosférica. Se separó el catalizador. Se evaporó el disolvente y se cromatografió el residuo por HPLC (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo) para dar 15,7 mg (71 %) del producto.

HPLC-MS (Método 1): tiempo de retención: 1,35 min

MS (ESI pos): m/z = 369 (M+H)+

Ejemplo 236



Se disolvieron 100 mg (73 %, 0,251 mmol) del ejemplo 40-5 en 2 mL de ácido acético y se añadieron 30 µL (0,35 mmol) de solución de peróxido de hidrógeno en agua (al 35 %). Se agitó la mezcla durante 3 h y se añadió acetonitrilo/agua. Se cromatografió la mezcla por HPLC (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo) para dar 50,3 mg (65 %) del producto.

HPLC-MS (Método 1): tiempo de retención: 0,88 min

MS (ESI pos): m/z = 307 (M+H)+

Ejemplo 237

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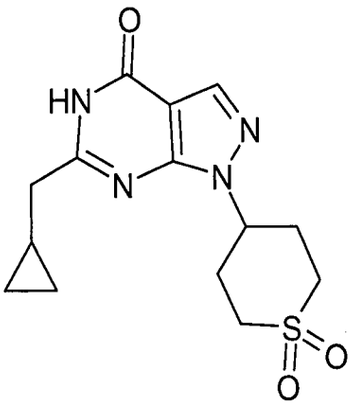

Se disolvieron 100 mg (73 %, 0,251 mmol) del ejemplo 40-5 en 2 mL de ácido acético y se añadieron 200 µL (2,33 mmol) de solución de peróxido de hidrógeno en agua (al 35 %). Se agitó la mezcla durante 3 días y se añadió acetonitrilo/agua. Se cromatografió la mezcla por HPLC (eluyente A: agua + 0,13 % de TFA, eluyente B: acetonitrilo) para dar 21,5 mg (27 %) del producto.

HPLC-MS (Método 1): tiempo de retención: 0,93 min

MS (ESI pos): m/z = 323 (M+H)+

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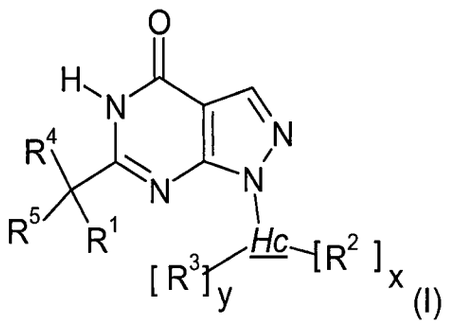
REIVINDICACIONES

1. Un compuesto según la fórmula general I



(I)

en la que

Hc es un grupo heterociclilo mono-, bi- o tricíclico, cuyos miembros del anillo son átomos de carbono y al menos 1, preferiblemente 1, 2 o 3, heteroátomos, que se seleccionan del grupo de nitrógeno, oxígeno y azufre, que está en la forma de $-S(O)_r$ - siendo r 0, 1 o 2, y

- dicho grupo heterociclilo es o comprende 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo y
- dicho grupo heterociclilo está unido a la estructura química (scaffold) por dicho 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo;

R^1 se selecciona del grupo de

alquil C_{1-8}-, alquenil C_{2-8}-, alquinil C_{2-8}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-

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alquil C_{1-6}-, aril-alquenil C_{2-6}-, aril-alquinil C_{2-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-alquenil C_{2-6}-, y heteroaril-alquinil C_{2-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-6}-O-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-O-, heteroaril-alquil C_{1-6}-O-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, piridin-2-ona-alquil C_{1-6}-O- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-O- estando el heterocicloalquilo C_{3-7} unido al O mediante uno de sus átomos C del anillo, heterocicloalquil C_{3-7}-alquil C_{1-6}-O- estando el heterocicloalquilo C_{3-7} unido al alquil C_{1-6}- mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-$(R^{10})N$-, R^{10}O-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y/o alquil C_{1-6}-SO_2-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-$(R^{10})N$-, R^{10}O-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-

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CO-O-, $(R^{10})_2N$-CO-$(R^{10})N$-, $(R^{10})_2N$-SO_2-$(R^{10})N$-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y/o alquil C_{1-6}-SO_2-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de:

H-, flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxi-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, preferiblemente alquil C_{1-6}-S-alquil C_{2-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, aril-alquenil C_{2-6}-, aril-alquinil C_{2-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-alquenil C_{2-6}-, heteroaril-alquinil C_{2-6}-, R^{10}-O-alquil C_{2-3}-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, R^{10}-O-CO-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-, alquil C_{1-6}-SO_2- y oxo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en

flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, alquil C_{1-6}-O-, alquil C_{1-6}-O-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-,

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este **R^2** será independientemente de cualquier otro **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-

alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-;

R^3 se selecciona del grupo de

H-, hidroxi y R^{10}-O-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, F_3C-, HF_2C-, FH_2C-, y alquil C_{1-3}-,

o

R^4 y R^5 junto con el átomo de carbono al que están unidos forman un grupo cicloalquilo de 3 a 6 miembros,

donde los miembros mencionados antes incluyendo el anillo carbocíclico formado, pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, alquil C_{1-6}-O- y (alquil C_{1-6}-)$_2$N-CO-;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

H- (pero no en el caso en que es parte de un grupo que se selecciona entre $R^{10}O$-CO-, R^{10}-SO_2- o R^{10}-CO-), F_3C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-3}-, heteroarilo, y heteroaril-alquil C_{1-3}-,

y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos $-CH_2-$ del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -S-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})-, preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2N-CO-$, estos dos R^{10} junto con dicho átomo de nitrógeno se unen para formar un grupo seleccionado del grupo de piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,

y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}- y alquil C_{1-6}-O-;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables,

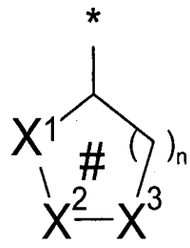
con la condición de que para cada realización aplicable de la fórmula I de la invención,

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un grupo $-CH_2-$.

2. Un compuesto según la reivindicación 1, en el que

Hc es un grupo heterociclilo según una fórmula que se selecciona del grupo de fórmulas I.1, I.2 y I.3:

fórmula I.1:



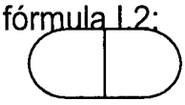
en la que

n = 1, 2, 3;

X^1, X^2, X^3, son independientemente uno de otro, CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, o $S(O)_r$ siendo r = 0, 1, 2, donde al menos uno de X^1, X^2, X^3 es O, NH, NR^2 o $S(O)_r$.

#: significa que el anillo no es aromático y cuando n = 1, un enlace dentro del sistema de anillos puede ser opcionalmente un doble enlace y cuando n = 2 o n = 3 un enlace o dos enlaces dentro del sistema de anillos pueden ser opcionalmente dobles enlaces, con los que se reemplazan los átomos de hidrógeno unidos a los miembros del anillo, donde tales dobles enlaces son preferiblemente un doble enlace C-C, y el anillo es más preferiblemente saturado;

fórmula I.2:



A ***B***

en la que

A es el sistema de anillos de la fórmula I.1;

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, $R^{10}O$-CO-O-, y/o $R^{10}O$-CO-$(R^{10})N$-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo-, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, bencil-O-, y/o $(R^{10})_2N$-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo y alquil C_{1-6}-,

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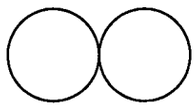
B es un segundo sistema de anillos de 3, 4, 5 o 6 miembros que está anillado con ***A*** y que aparte de los dos átomos y un enlace - que puede ser un enlace sencillo o doble - que comparte con ***A*** consiste solamente en átomos de carbono y que puede ser saturado, parcialmente saturado o aromático; los sustituyentes R^2 y/o R^3 independientemente uno de otro, e independientemente de cada x o y pueden estar en el anillo ***A*** o en el anillo ***B***; donde los dos átomos del anillo que son compartidos por los dos sistema de anillos ***A*** y ***B*** pueden ser ambos átomos de carbono, pueden ser ambos átomos de nitrógeno o uno puede ser un átomo de carbono y el otro puede ser un átomo de nitrógeno, donde son preferidos dos átomos de carbono o un átomo de carbono y un átomo de nitrógeno y son más preferidos dos átomos de carbono;

fórmula I.3:



A ***C***

en la que

A, es el sistema de anillos de la fórmula I.1;

C es un segundo sistema de anillos saturado o parcialmente saturado de 3, 4, 5 o 6 miembros que está espiro-condensado con ***A*** y que aparte del átomo que comparte con ***A*** consiste solamente en átomos de carbono y los sustituyentes R^2 y/o R^3 independientemente uno de otro, e independientemente de cada x e y pueden estar en el anillo ***A*** o en el anillo ***C***;

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo y heteroaril-alquil C_{1-6}-,

y en los casos en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este **R^2** será independientemente de cualquier otro **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, o alquil C_{1-6}-SO_2-, donde estos sustituyentes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor y alquil C_{1-6}-;

R^3 se selecciona del grupo de

H-, hidroxi, alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

H- (pero no en el caso en que es parte de un grupo que se selecciona entre $R^{10}O$-CO- o R^{10}-CO-), alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, arilo y heteroarilo,

y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos -CH_2- del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})-, preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2N$-CO-, estos dos R^{10} junto con dicho átomo de

nitrógeno se unen para formar un grupo seleccionado del grupo de piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,

y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

3. Un compuesto según la reivindicación 1, en el que

Hc es un grupo heterocíclico monocíclico, no aromático, saturado, de 4 a 8, preferiblemente 5, 6 o 7 átomos en el anillo, donde dichos átomos del anillo son átomos de carbono y 1, 2 o 3 heteroátomos, preferiblemente 1 heteroátomo, los heteroátomos se seleccionan entre oxígeno, nitrógeno y azufre, estando el azufre en la forma de – $S(O)_r$ - siendo r 0, 1 o 2, preferiblemente siendo r 0 y donde preferiblemente dicho grupo heterocíclico está unido a la estructura química mediante un átomo de carbono del anillo que no está unido directamente al heteroátomo del anillo;

$\mathbf{R^1}$ se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo y heteroaril-alquil C_{1-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, $R^{10}O$-CO-O-, y/o $R^{10}O$-CO-$(R^{10})N$-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, bencil-O-, y/o $(R^{10})_2N$-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que $\mathbf{R^2}$ está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este $\mathbf{R^2}$ será independientemente de cualquier otro $\mathbf{R^2}$: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

$\mathbf{R^3}$ se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

$\mathbf{R^4}$ y $\mathbf{R^5}$ independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente son ambos H;

$\mathbf{R^{10}}$ independientemente de cualquier otro $\mathbf{R^{10}}$ es alquil C_{1-6}-, fenilo, piridilo y en el caso en que $\mathbf{R^{10}}$ es un sustituyente de un átomo de nitrógeno de $\mathbf{R^{10}}$ se selecciona del grupo de H, alquil C_{1-6}-, fenilo y piridilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

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y sus sales farmacéuticamente aceptables,

con la condición de que

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún grupo CH_2- unido a dicho átomo de carbono.

4. Un compuesto según la reivindicación 1, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo y piperazinilo, más preferiblemente tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo, y de ellos preferiblemente, 3- y 4-tetrahidropiranilo, 3- y 4-piperidinilo y 3- pirrolidinilo;

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo y heteroaril-alquil C_{1-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno

de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, $R^{10}O$-CO-O-, y/o $R^{10}O$-CO-$(R^{10})N$-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo-, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, bencil-O-, y/o $(R^{10})_2N$-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

R^2 independientemente de cualquier otro **R^2** potencial se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este **R^2** será independientemente de cualquier otro **R^2**: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

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$\mathbf{R^4}$ y $\mathbf{R^5}$ independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son H;

$\mathbf{R^{10}}$ independientemente de cualquier otro $\mathbf{R^{10}}$ se selecciona del grupo de alquil C_{1-6}-, fenilo y piridilo y en el caso en que $\mathbf{R^{10}}$ es un sustituyente de un átomo de nitrógeno $\mathbf{R^{10}}$ se selecciona del grupo de H, alquil C_{1-6}-, fenilo y piridilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

5. Un compuesto según la reivindicación 1, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo y piperazinilo, donde preferiblemente el tetrahidropiranilo es 3- o 4-tetrahidropiranilo, el tetrahidrofuranilo es 3-tetrahidrofuranilo, y el piperidinilo es 3- o 4-piperidinilo; más preferiblemente ***Hc*** es tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo, y de ellos preferiblemente, 3- y 4-tetrahidropiranilo, 3- y 4-piperidinilo y 3- pirrolidinilo;

$\mathbf{R^1}$ se selecciona del grupo de

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fenilo, 2-, 3- y 4-piridilo, pirimidinilo, pirazolilo, tiazolilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-3}-O-, CF_3O-, CF_3-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, HO-alquil C_{1-6}-, oxadiazolilo, oxazolilo, isoxazolilo, triazolilo, tiazolilo, pirrolilo, furanilo, pirazolilo, piridilo, piridazinilo, pirimidinilo, $(R^{10})_2N$-CO-alquil C_{1-6}-, $(R^{10})_2N$-CO- y/o fenilo,

donde los grupos oxadiazolilo, oxazolilo, isoxazolilo, triazolilo, tiazolilo, pirrolilo, furanilo, pirazolilo, piridilo, piridazinilo, pirimidinilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CF_3-, CH_3O-, CF_3O-, H_2NCO-, NC-, morfolinilo y/o bencil-O-;

R^2 independientemente de cualquier otro **R^2** potencial se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que R^2 está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxilo y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de H, alquil C_{1-6}-, fenilo y piridilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x independientemente de cada uno de los otros **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cada uno de los otros **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

6. Un compuesto según la reivindicación 1, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo, piperazinilo, preferiblemente tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo, y de ellos preferiblemente, 3- y 4-tetrahidropiranilo, 3- y 4-piperidinilo y 3- pirrolidinilo;

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R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etilo, 1- y 2-propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3-, oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo, y/o fenilo,

donde los grupos oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CH_3O-, H_2NCO- y/o NC-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que R^2 está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este **R^2** será independientemente de cualquier otro **R^2**: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

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R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

7. Un compuesto según la reivindicación 1, en el que

Hc se selecciona del grupo de piperidinilo y pirrolidinilo, preferiblemente 3- o 4-piperidinilo y 3- pirrolidinilo;

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etilo, 1- y 2-propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3-, oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo, y/o fenilo,

donde los grupos oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CH_3O-, H_2NCO- y/o NC-;

$\mathbf{R^2}$ independientemente de cualquier otro $\mathbf{R^2}$ se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que $\mathbf{R^2}$ está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este $\mathbf{R^2}$ será independientemente de cualquier otro $\mathbf{R^2}$: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

$\mathbf{R^3}$ se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

$\mathbf{R^4}$ y $\mathbf{R^5}$ independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

8. Un compuesto según la reivindicación 1, en el que

Hc se selecciona del grupo de piperidinilo y pirrolidinilo, preferiblemente 3- o 4-piperidinilo y 3- pirrolidinilo;

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$\mathbf{R^1}$ se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3- y halógeno, y el halógeno se selecciona preferiblemente entre flúor, cloro y bromo.

$\mathbf{R^2}$ independientemente de cualquier otro $\mathbf{R^2}$ se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que $\mathbf{R^2}$ está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este $\mathbf{R^2}$ será independientemente de cualquier otro $\mathbf{R^2}$: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

$\mathbf{R^4}$ y $\mathbf{R^5}$ son ambos H

x = 0 o 1;

y = 0;

y sus sales farmacéuticamente aceptables.

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9. Un compuesto según la reivindicación 1, en el que

Hc se selecciona del grupo de tetrahidropiranilo y tetrahidrofuranilo, preferiblemente 3- o 4-tetrahidropiranilo y 3-tetrahidrofuranilo.

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etilo, 1- y 2-propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3-, oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo, y/o fenilo,

donde los grupos oxadiazolilo, triazolilo, pirazolilo, furanilo, piridilo y fenilo mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, CH_3-, CH_3O-, H_2NCO- y/o NC-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

donde los grupos alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R^3 se selecciona del grupo de

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H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, lo más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, lo más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

10, Un compuesto según la reivindicación 1, en el que

Hc se selecciona del grupo de tetrahidropiranilo y tetrahidrofuranilo, preferiblemente 3- o 4-tetrahidropiranilo y 3-tetrahidrofuranilo.

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3- y halógeno, y el halógeno se selecciona preferiblemente entre flúor, cloro y bromo.

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R² independientemente de cualquier otro **R²** se selecciona del grupo de H- y alquil C_{1-6}-,

donde los grupos alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

R³ se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R⁴ y **R⁵** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo, preferiblemente R^4 y R^5 son ambos H;

x independientemente de cualquier y: **x** = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, lo más preferiblemente **x** = 0;

y independientemente de cualquier x: **y** = 0, o 1, lo más preferiblemente **y** = 0;

y sus sales farmacéuticamente aceptables.

11. Un compuesto según la reivindicación 1, en el que

Hc se selecciona del grupo de tetrahidropiranilo y tetrahidrofuranilo, preferiblemente 3- o 4-tetrahidropiranilo y 3-tetrahidrofuranilo.

R¹ se selecciona del grupo de

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fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3- y halógeno, y el halógeno se selecciona preferiblemente entre flúor, cloro y bromo.

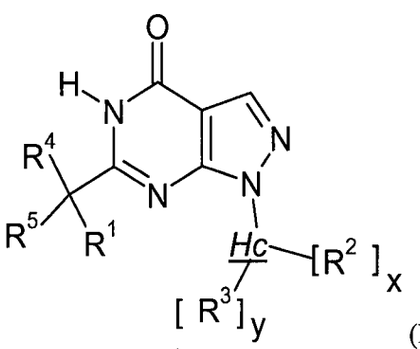
R^4 y **R^5** son ambos H

x = 0;

y = 0;

y sus sales farmacéuticamente aceptables.

12. Un compuesto según la fórmula general I de la reivindicación 1



(I),

en la que;

Hc es un grupo heterociclilo mono-, bi- o tricíclico, cuyos miembros del anillo son átomos de carbono y al menos 1, preferiblemente 1, 2 o 3, heteroátomos, que se seleccionan del grupo de nitrógeno, oxígeno y azufre, que está en la forma de $-S(O)_r$ - siendo r 0, 1 o 2, y

- dicho grupo heterociclilo es o comprende 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo y

- dicho grupo heterociclilo está unido a la estructura química (scaffold) por dicho 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo.

R^1 se selecciona del grupo de

alquil C_{1-8}-, alquenil C_{2-8}-, alquinil C_{2-8}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, y heteroaril-alquil C_{1-6}-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-6}-O-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-O-, heteroaril-alquil C_{1-6}-O-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-O- estando el heterocicloalquilo C_{3-7} unido al O mediante uno de sus átomos C del anillo, heterocicloalquil C_{3-7}-alquil C_{1-6}-O- estando el heterocicloalquilo C_{3-7} unido al alquil C_{1-6}- mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-$(R^{10})N$-, R^{10}O-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-

SO_2-(R^{10})N-alquil C_{1-6}-, (R^{10})$_2$N-SO_2-(R^{10})N-alquil C_{1-6}-, (R^{10})$_2$N-SO_2-, (R^{10})$_2$N-SO_2-alquil C_{1-6}-, y alquil C_{1-6}-SO_2-,

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo mencionados antes pueden estar opcionalmente sustituidos con HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, (R^{10})$_2$N-, (R^{10})$_2$N-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, (R^{10})$_2$N-CO-, (R^{10})$_2$N-CO-alquil C_{1-6}-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-(R^{10})N-, R^{10}O-CO-(R^{10})N-alquil C_{1-6}-, (R^{10})$_2$N-CO-O-, (R^{10})$_2$N-CO-(R^{10})N-, (R^{10})$_2$N-SO_2-(R^{10})N-, (R^{10})$_2$N-CO-O-alquil C_{1-6}-, (R^{10})$_2$N-CO-(R^{10})N-alquil C_{1-6}-, R^{10}-SO_2-(R^{10})N-, R^{10}-SO_2-(R^{10})N-alquil C_{1-6}-, (R^{10})$_2$N-SO_2-(R^{10})N-alquil C_{1-6}-, (R^{10})$_2$N-SO_2-, (R^{10})$_2$N-SO_2-alquil C_{1-6}-, o alquil C_{1-6}-SO_2-.

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxi-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{2-3}-, (R^{10})$_2$N-, R^{10}O-CO-, (R^{10})$_2$N-CO-, R^{10}-CO-(R^{10})N-, R^{10}-CO-, (R^{10})$_2$N-CO-(R^{10})N-, R^{10}-SO_2-(R^{10})N-, y alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, alquil C_{1-6}-O-alquil C_{1-6}-, alquil C_{1-6}-, (R^{10})$_2$N-, (R^{10})$_2$N-alquil C_{1-3}-, y (R^{10})$_2$N-CO-,

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y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, **este R^2** será independientemente de cualquier otro **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, R^{10}-SO_2-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-3}-, y $(R^{10})_2N$-CO-;

R^3 se selecciona independientemente del grupo de H-, hidroxi y R^{10}-O-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, F_3C-, HF_2C-, FH_2C-, y alquil C_{1-3}-,

o

R^4 y R^5 junto con el átomo de carbono al que están unidos forman un grupo cicloalquilo de 3 a 6 miembros,

donde los miembros mencionados antes incluyendo el anillo carbocíclico formado, pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, HO-, NC-, O_2N-,

F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, alquil C_{1-6}-O- y (alquil C_{1-6}-)$_2$N-CO-;

R^{10} independientemente de cualquier otro **R^{10}** se selecciona del grupo de

H- (pero no en el caso en que es parte de un grupo que se selecciona entre R^{10}O-CO-, R^{10}-SO_2- o R^{10}-CO-), F_3C-CH_2-, alquil C_{1-6}-, alquenil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, arilo, aril-alquil C_{1-3}-, heteroarilo, y heteroaril-alquil C_{1-3}-,

y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos -CH_2- del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -S-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})- preferiblemente, y en particular preferiblemente en el caso de (R^{10})$_2$N-CO-, estos dos grupos R^{10} junto con dicho átomo de nitrógeno se unen para formar un grupo seleccionado entre piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,
y donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, HO-alquil C_{1-6}-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}- y alquil C_{1-6}-O-;

x = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, lo más preferiblemente **x** = 0;

y = 0, o 1, lo más preferiblemente **y** = 0;

y sus formas salinas o solvatos farmacéuticamente aceptables,

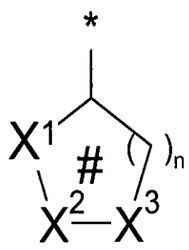
con la condición de que

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador $-CH_2-$.

13. Un compuesto según la reivindicación 12, en el que

Hc es un grupo heterociclilo según una fórmula que se selecciona del grupo de fórmulas I.1, I.2 y I.3:

fórmula I.1:



en la que

n = 1, 2, 3;

X^1, X^2, X^3, independientemente uno de otro, son CH_2, CHR^2, CHR^3, $C(R^2)_2$, CR^2R^3, O, NH, NR^2, o $S(O)_r$ siendo r = 0, 1, 2, donde al menos uno de X^1, X^2, X^3 es O, NH, NR^2 o $S(O)_r$.;

#: significa que el anillo no es aromático y cuando n = 1, un enlace dentro del sistema de anillos puede ser opcionalmente un doble enlace y cuando n = 2 o n = 3 un enlace o dos enlaces dentro del sistema de anillos pueden ser opcionalmente dobles enlaces, con los que se reemplazan los átomos de hidrógeno unidos a los miembros del anillo, donde tales dobles enlaces son preferiblemente un doble enlace C-C, y el anillo es más preferiblemente saturado;

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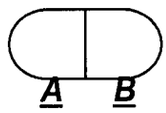
fórmula I.2:

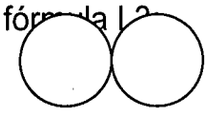


en la que

A es el sistema de anillos de la fórmula I.1;

B es un segundo sistema de anillos de 3, 4, 5 o 6 miembros que está anillado con ***A*** y que aparte de los dos átomos y un enlace - que puede ser un enlace sencillo o doble - que comparte con ***A*** consiste solamente en átomos de carbono y que puede ser saturado, parcialmente saturado o aromático; los sustituyentes R^2 y/o R^3 independientemente uno de otro, e independientemente de cada x o y pueden estar en el anillo ***A*** o en el anillo ***B***; donde los dos átomos del anillo que son compartidos por los dos sistema de anillos ***A*** y ***B*** pueden ser ambos átomos de carbono, pueden ser ambos átomos de nitrógeno o uno puede ser un átomo de carbono y el otro puede ser un átomo de nitrógeno, donde son preferidos dos átomos de carbono o un átomo de carbono y un átomo de nitrógeno y son más preferidos dos átomos de carbono;

fórmula I.3



en la que

A, es el sistema de anillos de la fórmula I.1;

C es un segundo sistema de anillos saturado o parcialmente saturado de 3, 4, 5 o 6 miembros que está espiro-condensado con ***A*** y que aparte del átomo que comparte con ***A*** consiste solamente en átomos de carbono y los sustituyentes R^2 y/o R^3

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independientemente uno de otro, e independientemente de cada x e y pueden estar en el anillo ***A*** o en el anillo ***C***;

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, arilo y heteroarilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, $R^{10}O$-CO-O-, y $R^{10}O$-CO-$(R^{10})N$-;

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo, mencionados antes pueden estar opcionalmente sustituidos con NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, $R^{10}O$-CO-, o $(R^{10})_2N$-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), $(R^{10})_2N$-CO-, R^{10}-CO-$(R^{10})N$-,

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donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo y alquil C_{1-6}-,

y en el caso en que $\mathbf{R^2}$ está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este $\mathbf{R^2}$ será independientemente de cualquier otro $\mathbf{R^2}$: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor y alquil C_{1-6}-;

$\mathbf{R^3}$ independientemente de cualquier otro $\mathbf{R^3}$ se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-; preferiblemente $\mathbf{R^3}$ es H-;

$\mathbf{R^4}$ y $\mathbf{R^5}$ independientemente uno de otro, se selecciona del grupo de H-, flúor, y metilo; preferiblemente independientemente uno de otro, son H- o flúor, más preferiblemente $\mathbf{R^4}$ y $\mathbf{R^5}$ son ambos H;

$\mathbf{R^{10}}$ independientemente de cualquier otro $\mathbf{R^{10}}$ potencial se selecciona del grupo de

alquil C_{1-6}-, cicloalquil C_{3-7}-, arilo y heteroarilo,

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y en el caso en que dos grupos R^{10} estén ambos unidos al mismo átomo de nitrógeno ellos pueden formar junto con dicho átomo de nitrógeno un anillo heterocicloalquilo de 3 a 7 miembros, y donde uno de los grupos $-CH_2-$ del anillo heterocicloalquilo formado puede ser reemplazado por -O-, -NH-, -N(cicloalquil C_{3-6})-, -N(cicloalquil C_{3-6}-alquil C_{1-4})- o -N(alquil C_{1-4})- preferiblemente, y en particular preferiblemente en el caso de $(R^{10})_2N-CO-$, estos dos R^{10} junto con dicho nitrógeno se unen para formar un grupo seleccionado entre piperidinilo, piperazinilo, pirrolidinilo, morfolinilo y tiomorfolinilo,

y

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil $C_{1-6}-O-$;

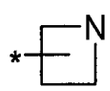
x = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, lo más preferiblemente **x** = 0;

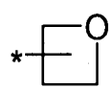
y = 0, o 1, lo más preferiblemente **y** = 0;

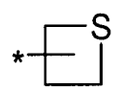
y sus sales o solvatos farmacéuticamente aceptables.

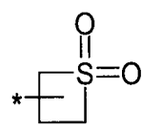
14. Un compuesto según la reivindicación 12, en el que

Hc es un grupo heterociclilo seleccionado del grupo de









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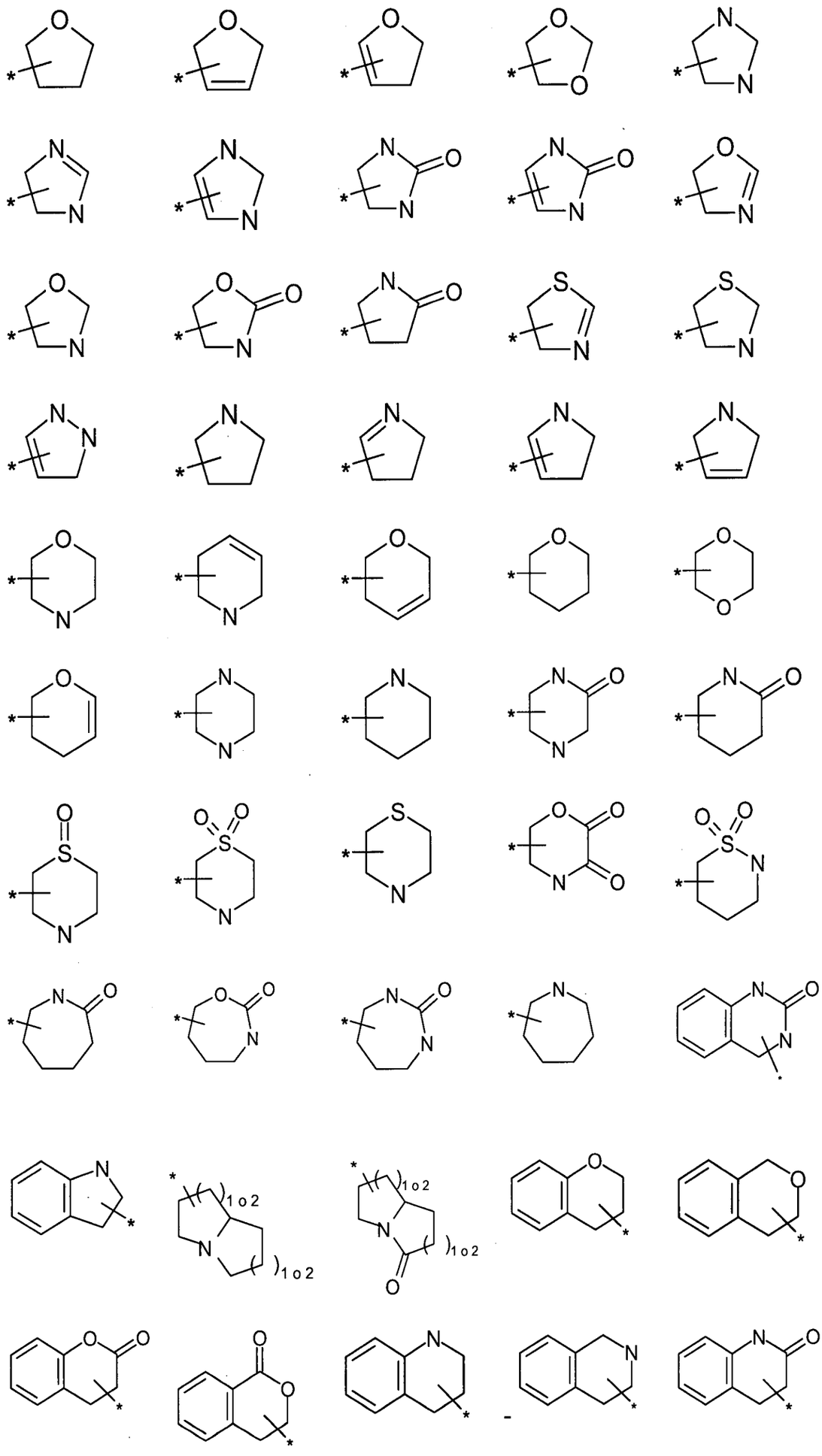
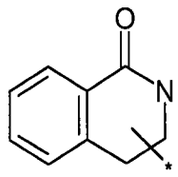
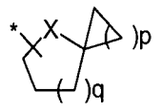
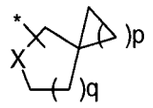


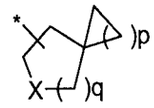




X = O, S o N
p = 1, 2, 3, 4 o 5
q = 1, 2 o 3



X = O, S o N
p = 1, 2, 3, 4 o 5
q = 1, 2 o 3



X = O, S o N
p = 1, 2, 3, 4 o 5
q = 1, 2 o 3

R^1 se selecciona del grupo de

alquil C_{1-8}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-3}-, heterocicloalquil C_{3-7}-, arilo y heteroarilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, tetrahidrofuranil-O-, tetrahidropiranil-O-, piperidinil-O- estando el piperidinilo unido al O mediante uno de sus átomos C del anillo, pirrolidinil-O- estando el pirrolidinilo unido al O mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-(R^{10})N-, R^{10}-CO-(R^{10})N-alquil C_{1-6}-, R^{10}O-CO-O-, y R^{10}O-CO-(R^{10})N-;

donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, tetrahidrofuranilo, tetrahidropiranilo, piperidinilo, pirrolidinilo, mencionados antes pueden estar opcionalmente sustituidos con NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, R^{10}-O-alquil C_{1-6}-, alquil C_{1-6}-, R^{10}-O-, R^{10}-CO-, R^{10}O-CO-, o $(R^{10})_2N$-CO-, donde los piperidinilo o pirrolidinilo preferiblemente están sustituidos con R^{10}-CO-;

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R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de

H-, flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, alquil C_{1-6}- (preferiblemente alquilo C_{2-6}), $(R^{10})_2N$-CO-, R^{10}-CO-(R^{10})N-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, cloro, bromo y alquil C_{1-6}-,

y en el caso en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este **R^2** será independientemente de cualquier otro **R^2**: H-, F_3C-CH_2-, HF_2C-CH_2-, alquil C_{1-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, R^{10}-O-alquil C_{1-3}-, R^{10}O-CO-, $(R^{10})_2N$-CO-, R^{10}-CO-, o alquil C_{1-6}-SO_2-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor y alquil C1-6-;

R^3 se selecciona del grupo de

independientemente de cualquier otro R^3: H-, hidroxilo y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-;

R^4 y **R^5** independientemente uno de otro, se seleccionan del grupo de H-, flúor, y metilo; preferiblemente independientemente uno de otro, se seleccionan del grupo de H- y flúor, más preferiblemente **R^4** y **R^5** son ambos H;

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$\mathbf{R^{10}}$ independientemente de cualquier otro $\mathbf{R^{10}}$ se selecciona del grupo de

alquil C_{1-6}-, cicloalquil C_{3-7}-, arilo y heteroarilo,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-;

x = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, lo más preferiblemente **x** = 0;

y = 0, o 1, lo más preferiblemente **y** = 0;

y sus sales o solvatos farmacéuticamente aceptables

con la condición de que

si ***Hc*** es oxetanilo, que está unido mediante el átomo de carbono próximo al oxígeno del oxetanilo, no hay ningún sustituyente unido a dicho átomo de carbono mediante un separador -CH_2-.

15. Un compuesto según la reivindicación 13, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo;

y

$\mathbf{R^2}$ independientemente de cualquier otro $\mathbf{R^2}$ se selecciona del grupo de H- y alquil C_{1-6}-,

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y en los casos en que R^2 está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este R^2 será independientemente de cualquier otro R^2: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

y

R^4 y R^5 son H

y

R^{10} independientemente de cualquier otro R^{10} se selecciona del grupo de alquil C_{1-6}-, fenilo, y piridilo

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes seleccionados del grupo que consiste en flúor, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, CH_3-O-alquil C_{1-6}-, alquil C_{1-6}-, y alquil C_{1-6}-O-.

16. Un compuesto según la reivindicación 15, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo;

y

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, pirimidinilo, pirazolilo, tiazolilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados del grupo que consiste en HO-, NC-, alquil C_{1-6}-O-,

alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-3}-O-, CF_3O-, CF_3-, flúor, cloro, bromo, heterocicloalquil C_{3-7}- y heterocicloalquil C_{3-7}-alquil C_{1-6}-.

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este **R^2** será independientemente de cualquier otro **R^2**: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

y

R^3 independientemente de cualquier otro **R^3** se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-; preferiblemente **R^3** es H-;

y

R^4 y R^5 son H

y

x = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, lo más preferiblemente **x** = 0;

y = 0, o 1, lo más preferiblemente **y** = 0;

y sus sales o solvatos farmacéuticamente aceptables.

17. Un compuesto según la reivindicación 1, en el que

Hc se selecciona del grupo de tetrahidropiranilo, tetrahidrofuranilo, piperidinilo, pirrolidinilo;

y

R^1 se selecciona del grupo de

fenilo, 2-, 3- y 4-piridilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentilmetilo, etilo, propilo, 1- y 2-butilo, 1-, 2- y 3-pentilo, tetrahidrofuranilo, y tetrahidropiranilo,

donde estos grupos pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados del grupo que consiste en NC-, alquil C_{1-6}-O-, alquil C_{1-6}-, CF_3O-, CF_3- y halógeno, y el halógeno se selecciona preferiblemente del grupo de flúor, cloro y bromo.

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de H- y alquil C_{1-6}-,

y en los casos en que **R^2** está unido a un nitrógeno que es un miembro del anillo de ***Hc***, este **R^2** será independientemente de cualquier otro **R^2**: H-, alquil C_{1-6}-CO-, alquil C_{1-6}-O-CO-, alquil C_{1-6}-, fenil-CO-, fenil-O-CO-, (alquil C_{1-6}-)$_2$N-CO-,

donde los miembros mencionados antes pueden estar opcionalmente sustituidos, independientemente uno de otro, con uno o más sustituyentes flúor;

y

R^3 independientemente de cualquier otro **R^3** se selecciona del grupo de

H-, hidroxi y alquil C_{1-6}-O-, donde el alquil C_{1-6}-O- puede estar opcionalmente sustituido con uno o más flúor, cloro, bromo y HO-; preferiblemente **R^3** es H-;

y

R^4 y R^5 son H

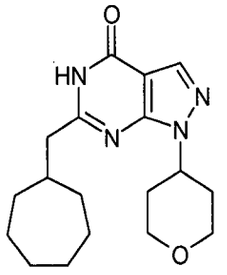
Y

x = 0, 1, 2, 3 o 4, preferiblemente **x** = 0, 1 o 2, preferiblemente **x** = 0 o 1, lo más preferiblemente **x** = 0;

y = 0, o 1, lo más preferiblemente **y** = 0;

y sus sales o solvatos farmacéuticamente aceptables.

18. Un compuesto según la reivindicación 1, caracterizado porque el compuesto se selecciona del grupo de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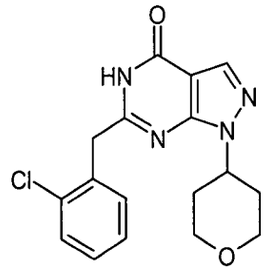
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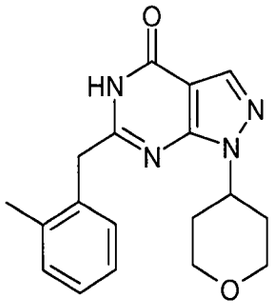
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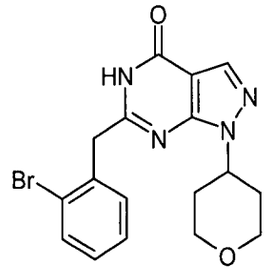
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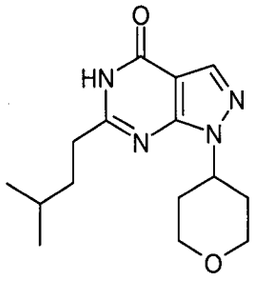
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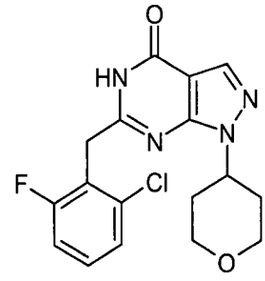
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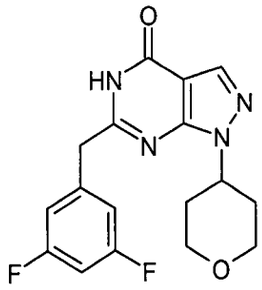

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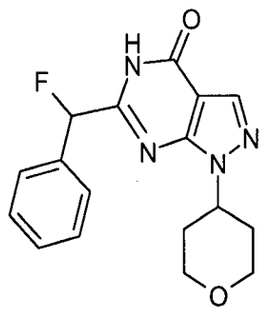

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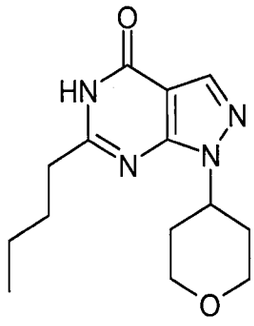

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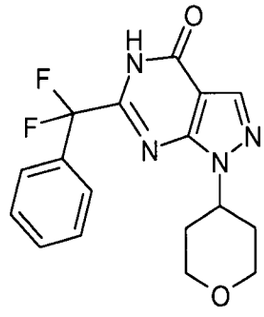

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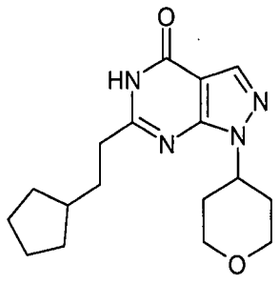

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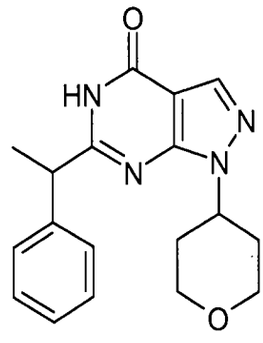

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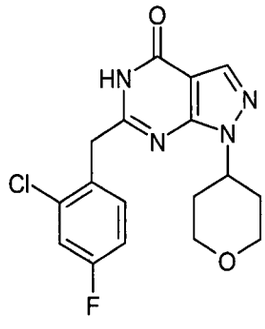

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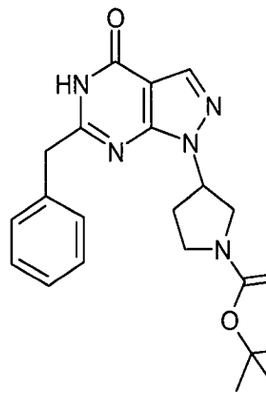

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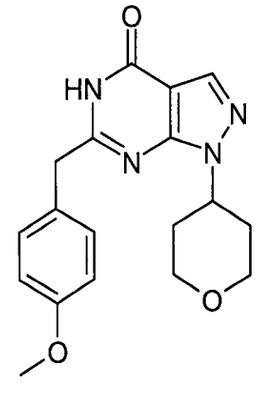

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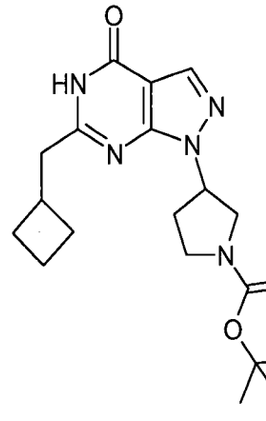

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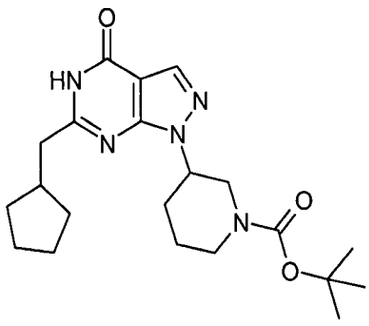

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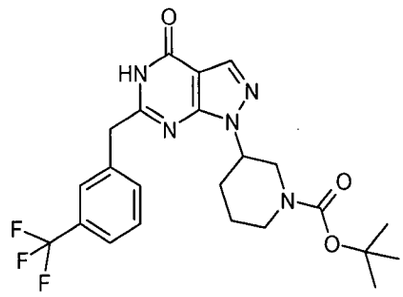

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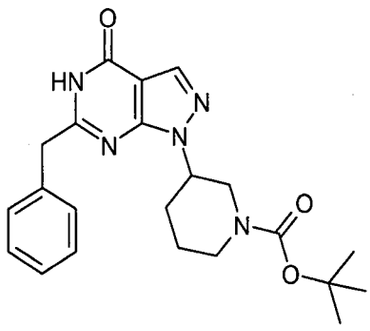

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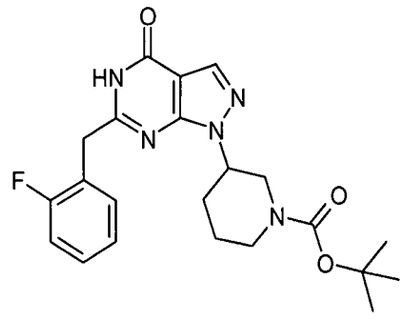

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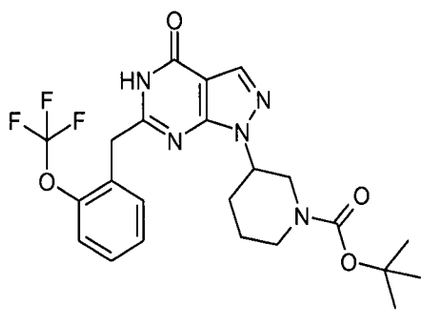

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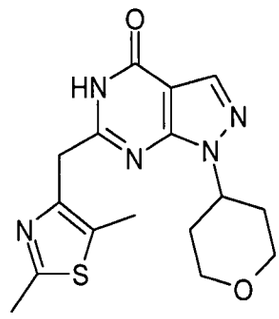

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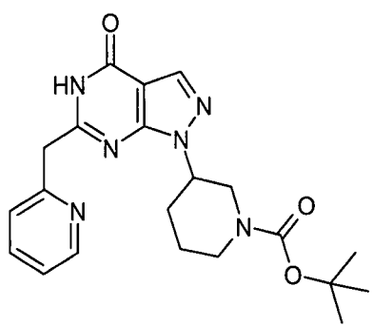

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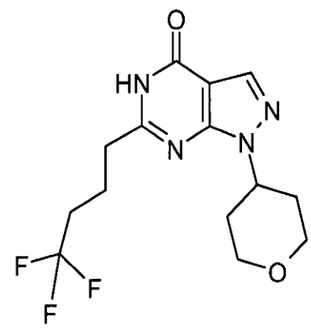

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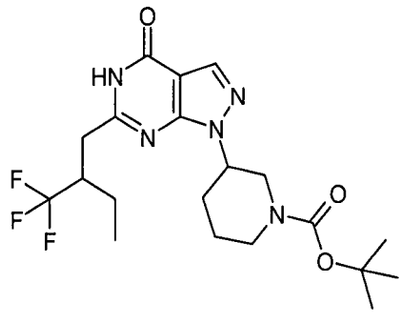

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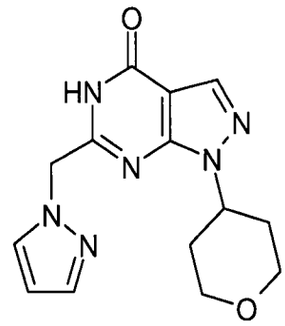

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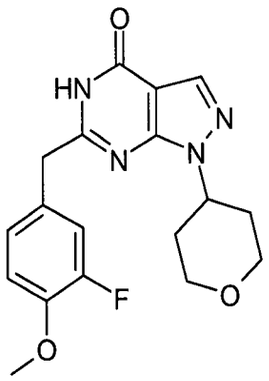

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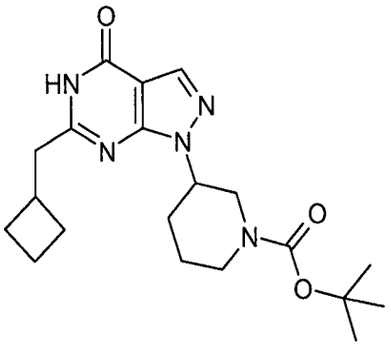

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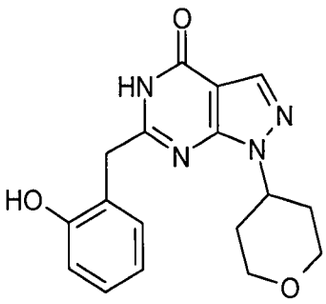

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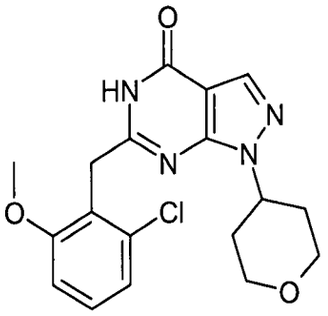

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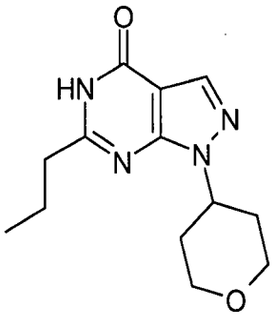

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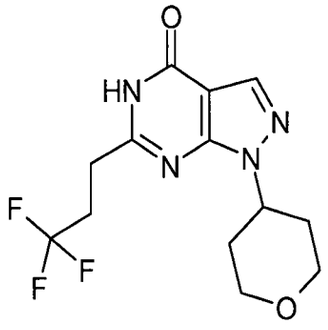

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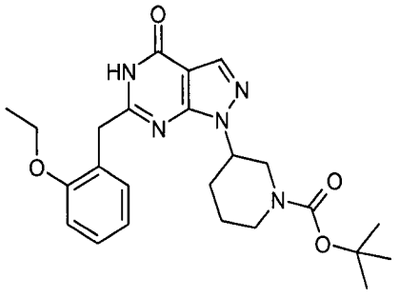

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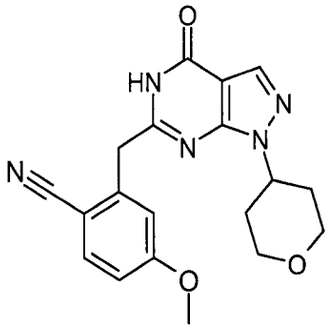

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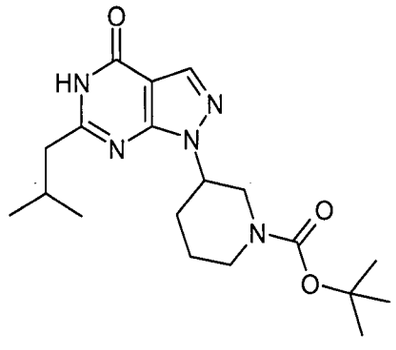

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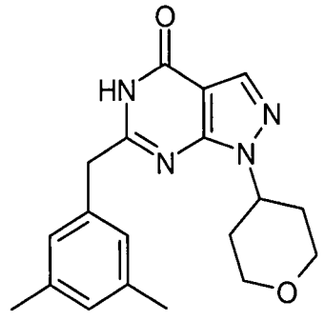

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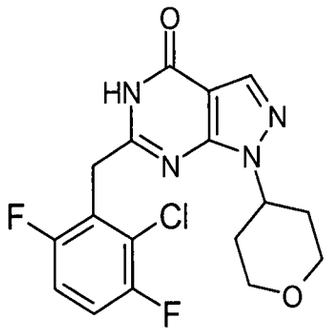

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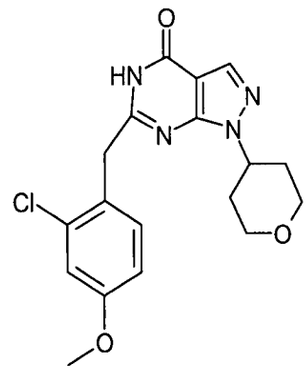

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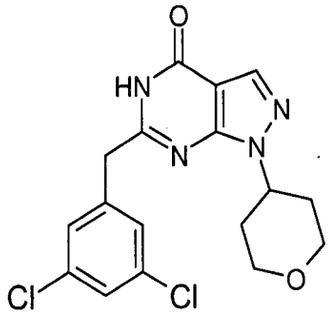

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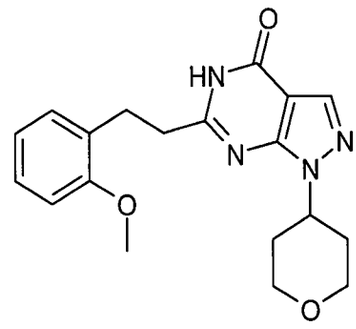

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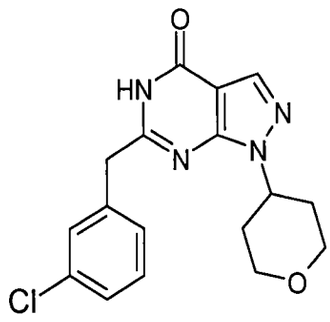

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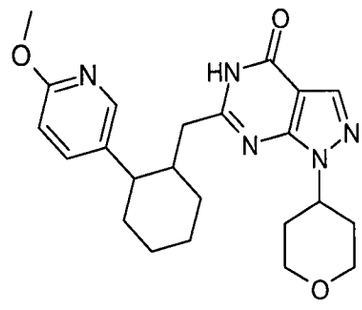

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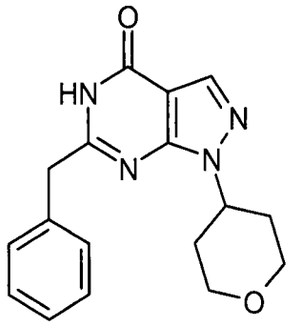

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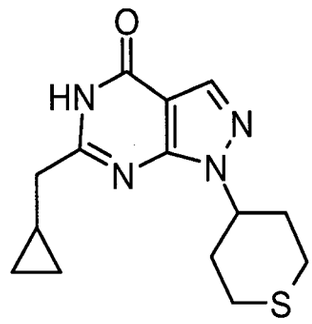

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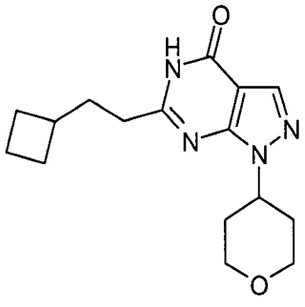

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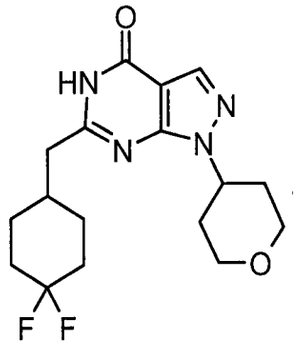

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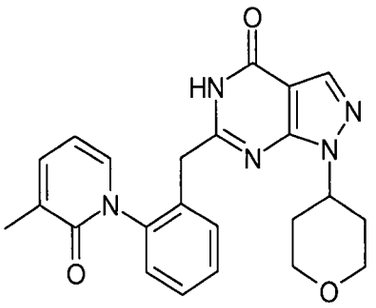
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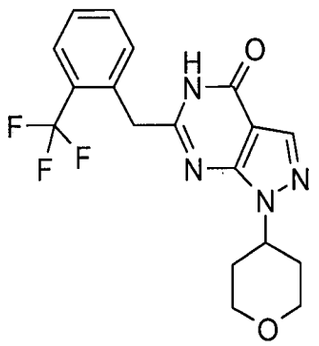
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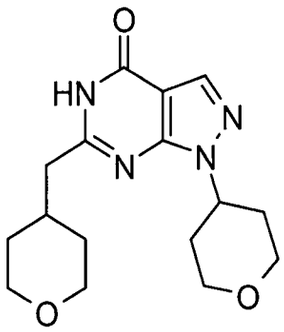
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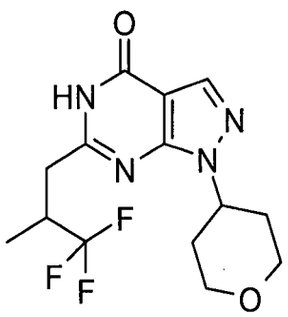
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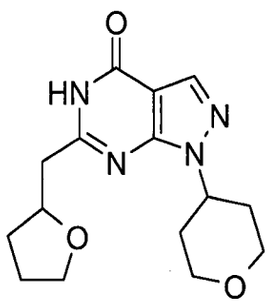
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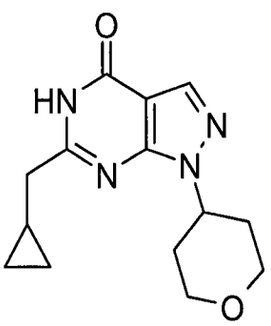
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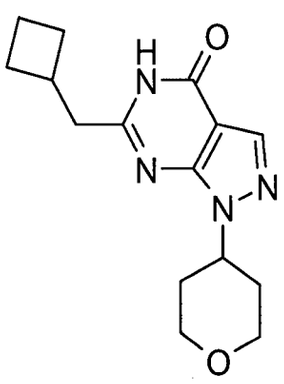
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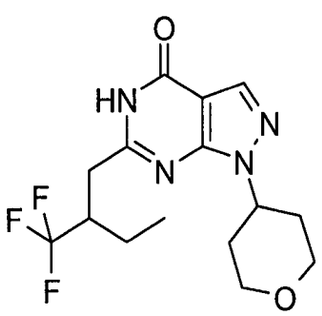
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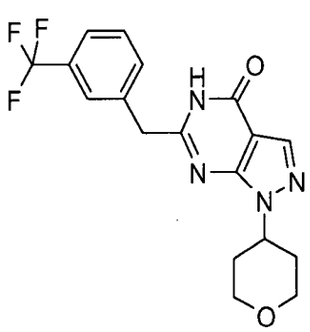
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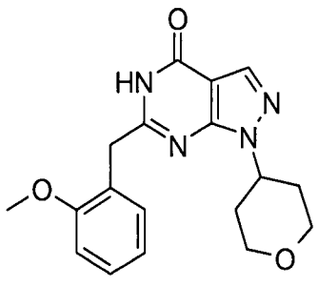
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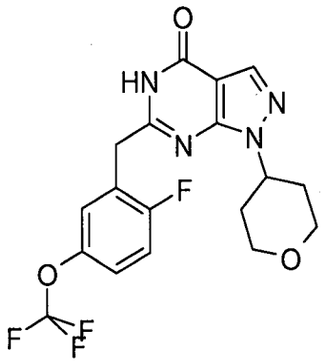

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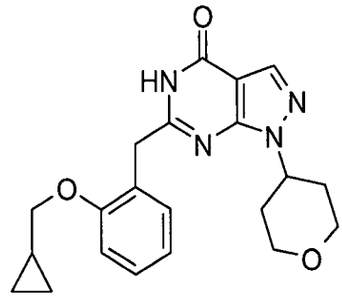

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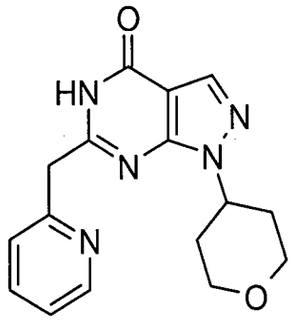

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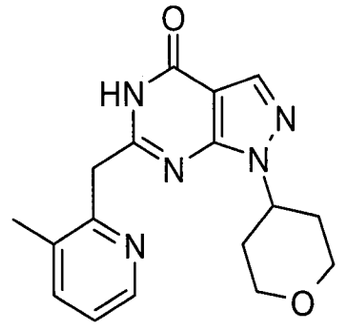

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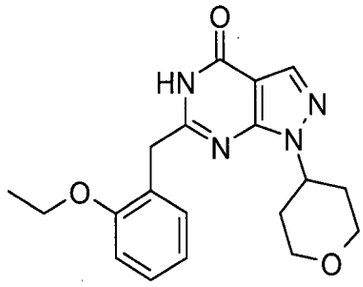

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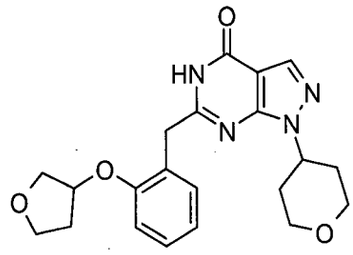

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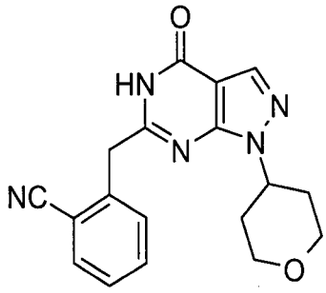

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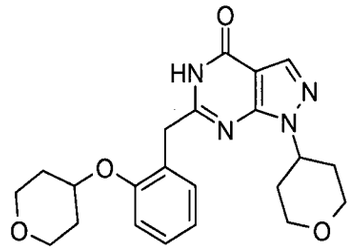

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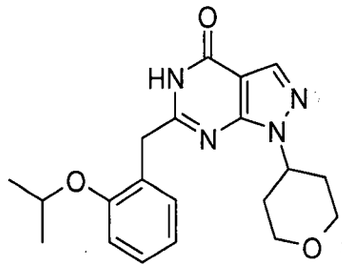

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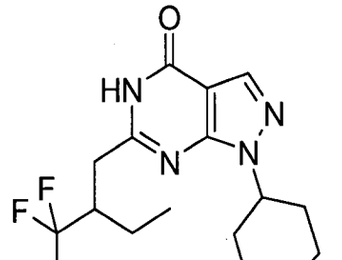

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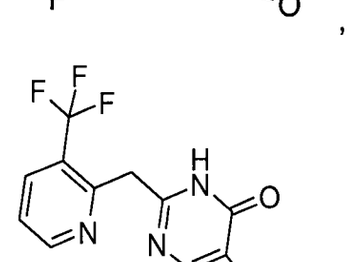

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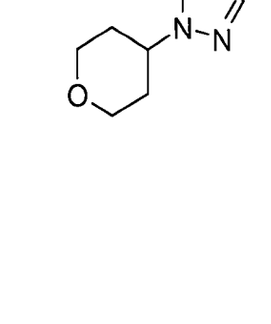

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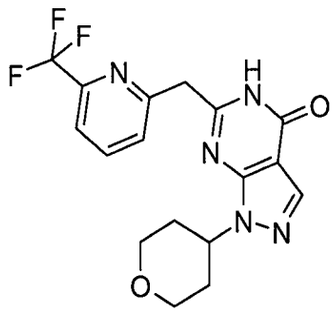

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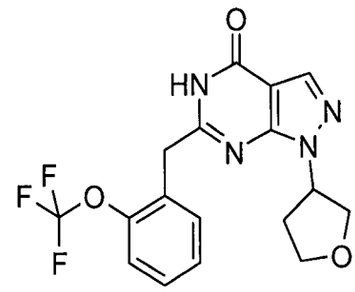

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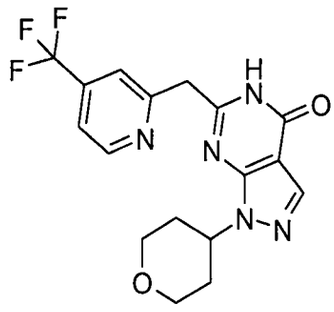

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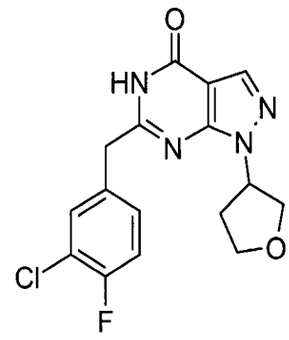

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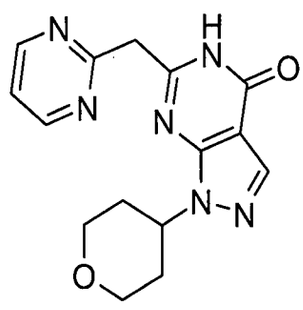

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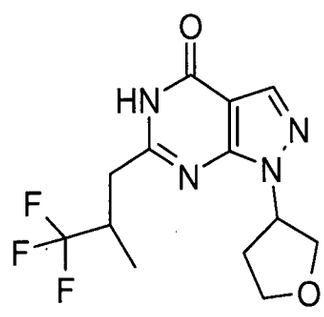

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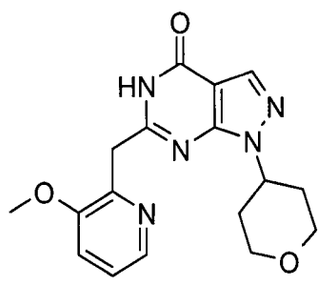

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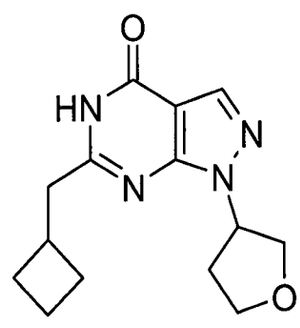

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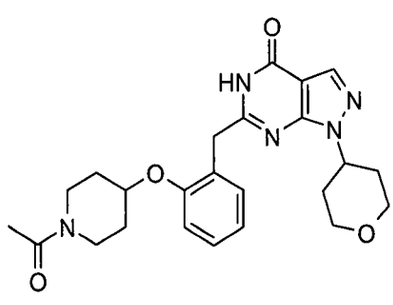

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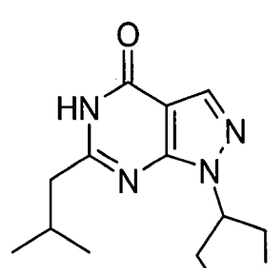

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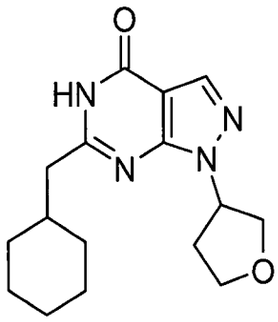

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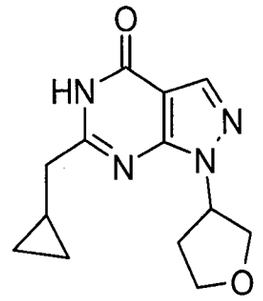

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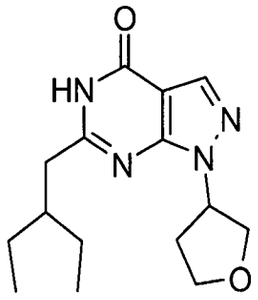

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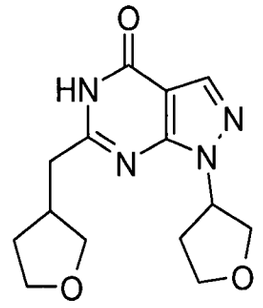

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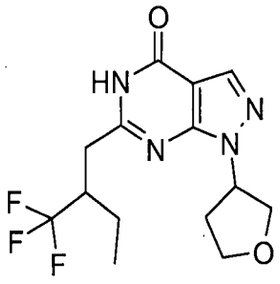

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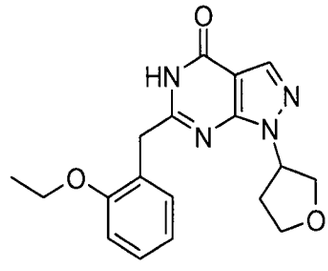

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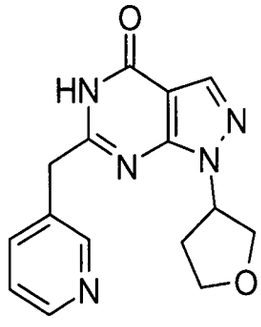

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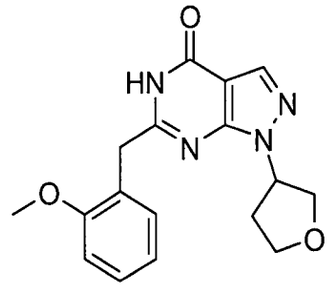

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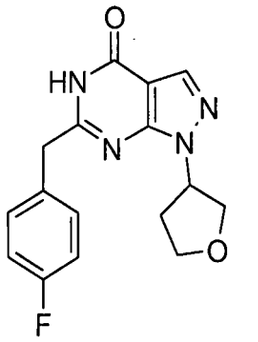

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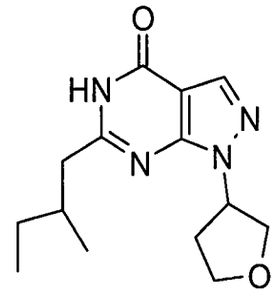

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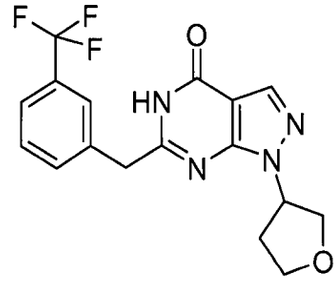

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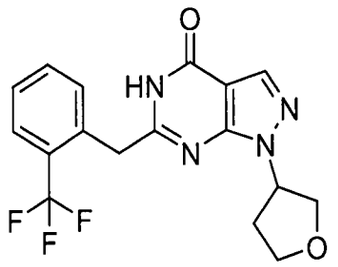
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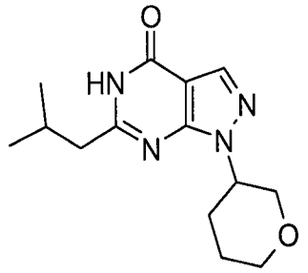
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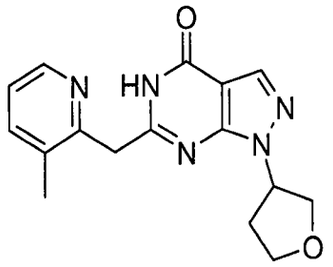
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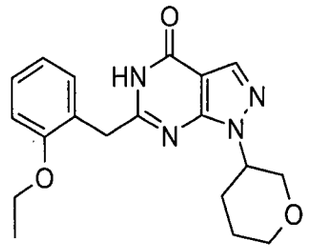
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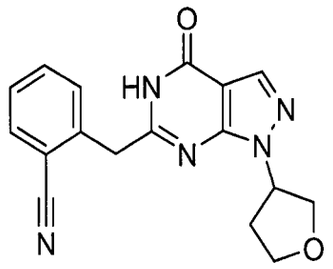
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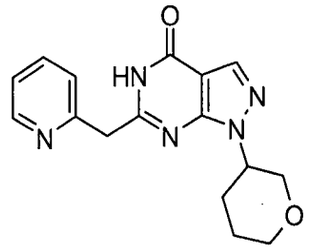
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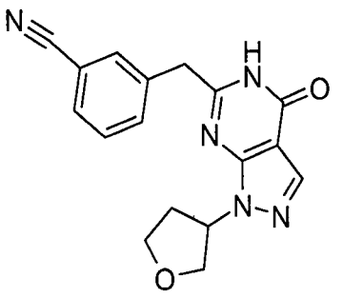
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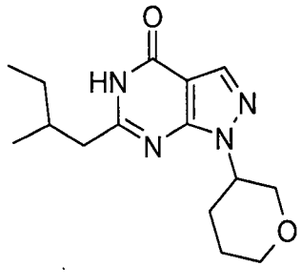
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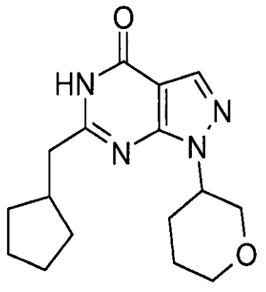
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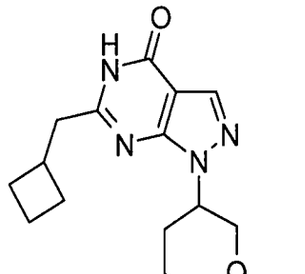
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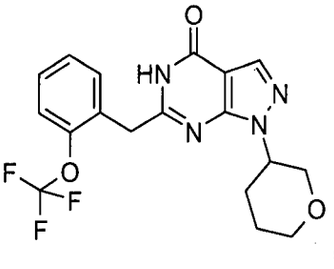
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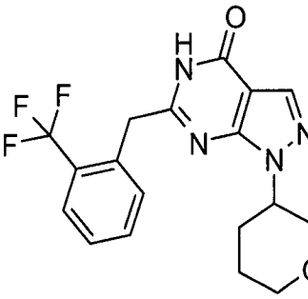
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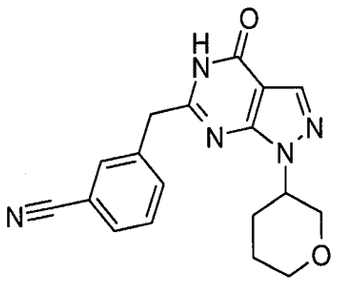

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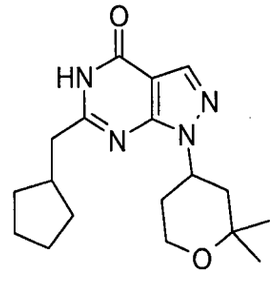

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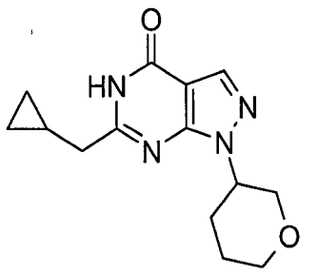

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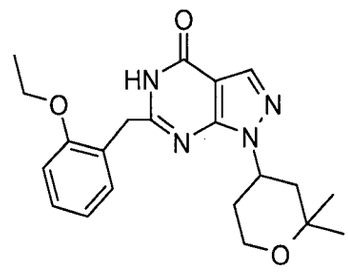

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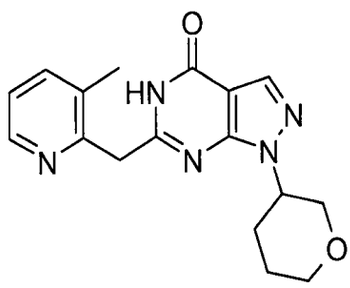

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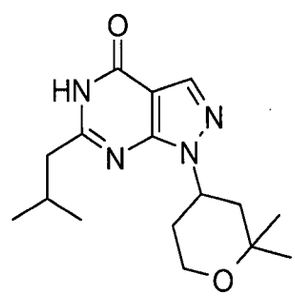

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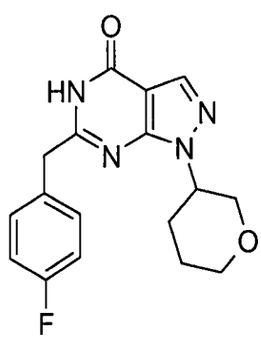

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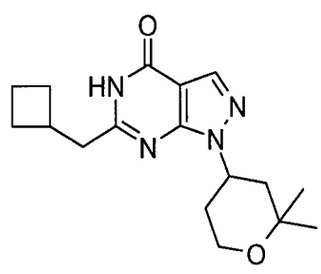

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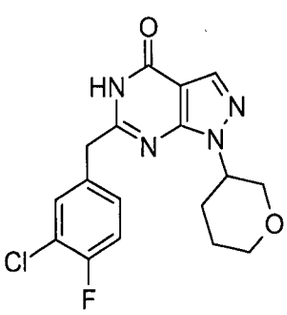

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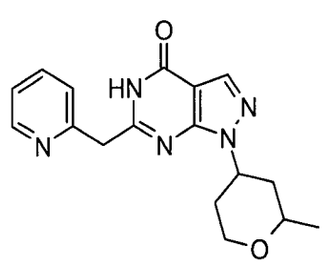

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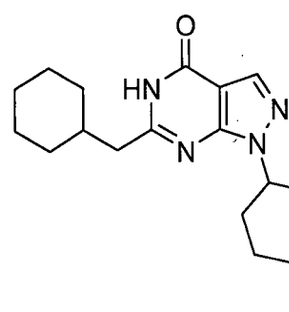

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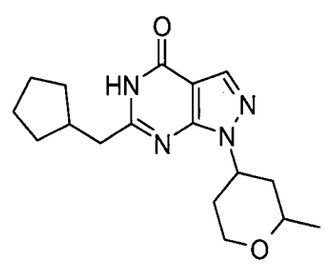

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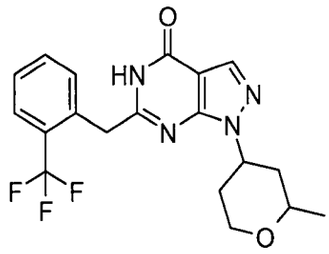

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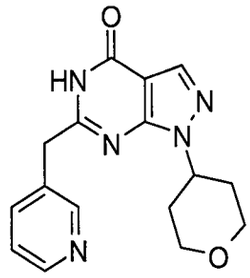

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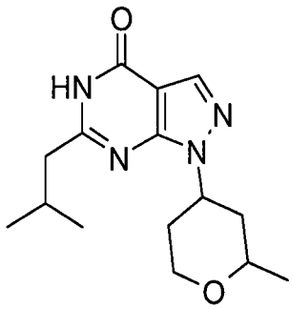

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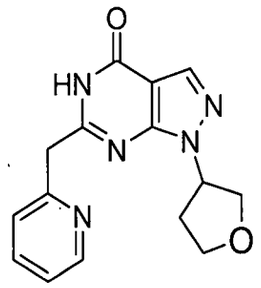

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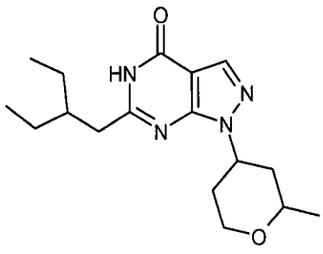

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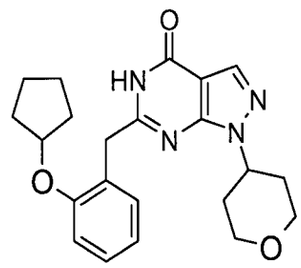

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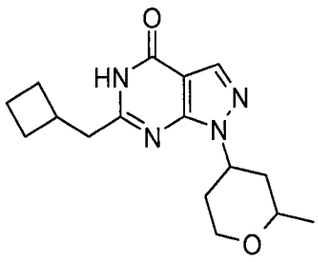

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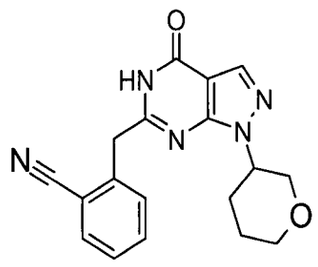

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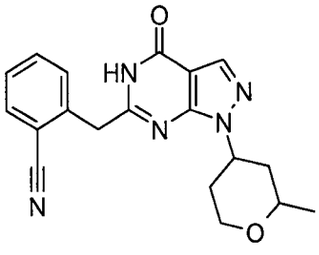

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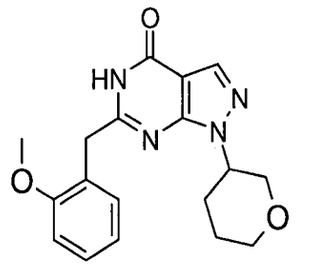

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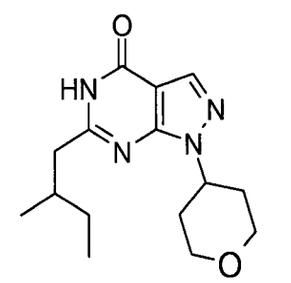

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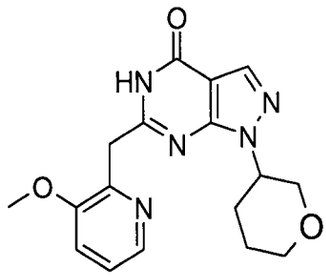

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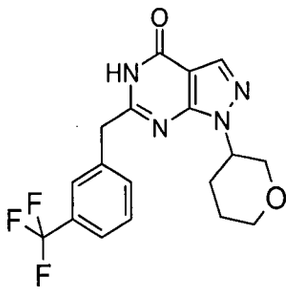

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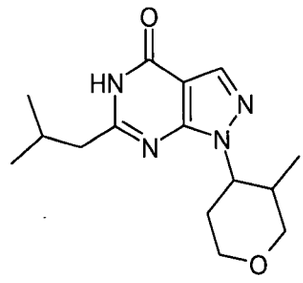

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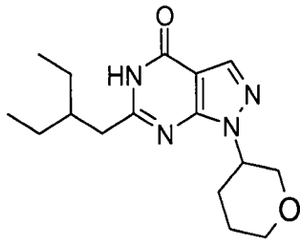

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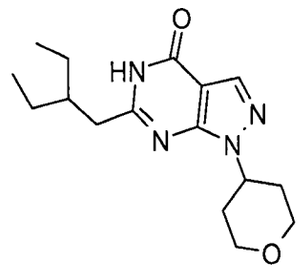

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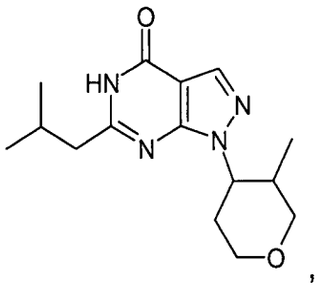

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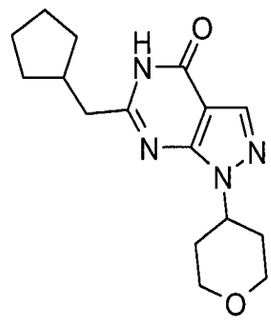

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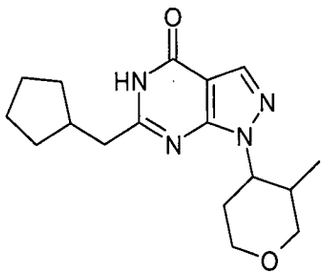

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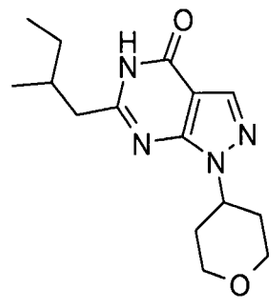

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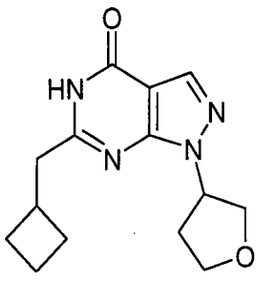

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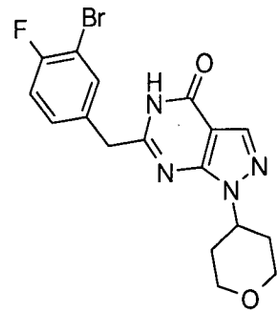

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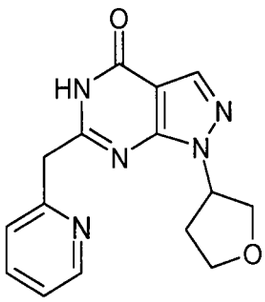

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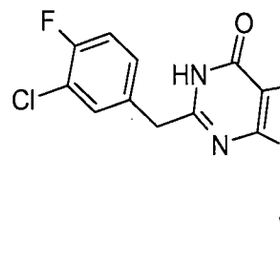

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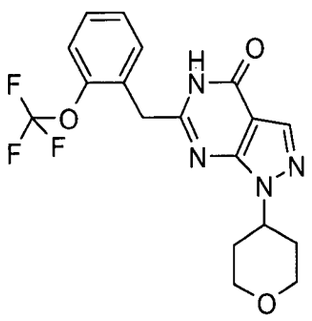

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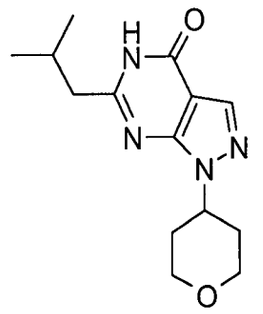

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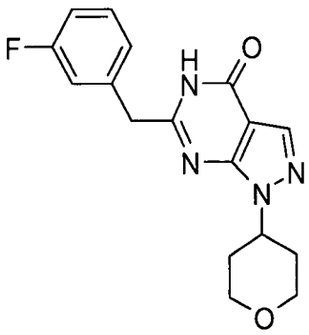

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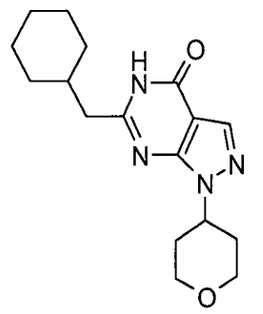

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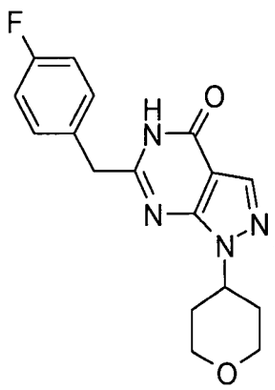

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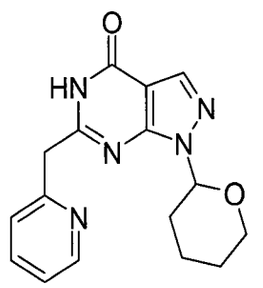

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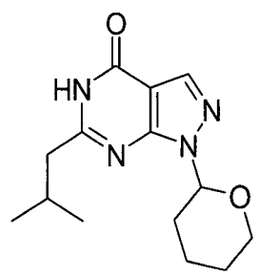

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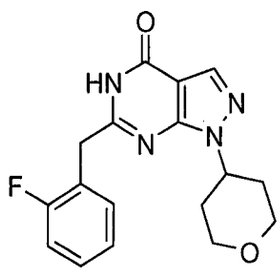

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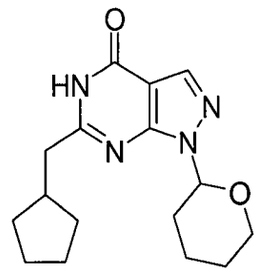

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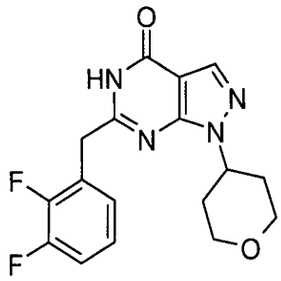

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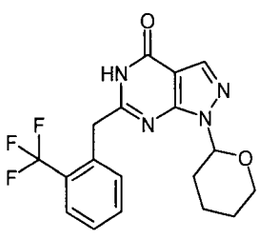

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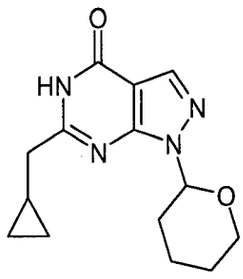

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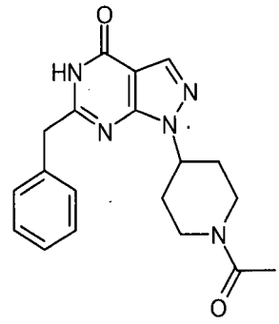

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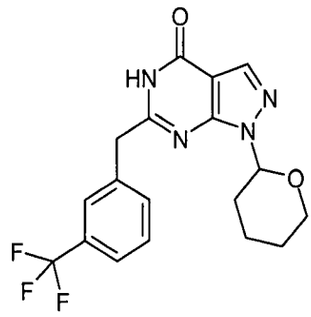

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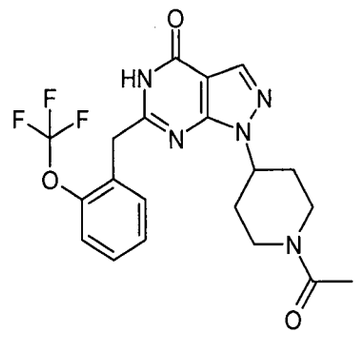

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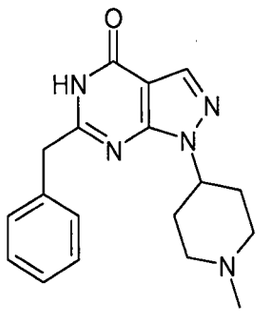

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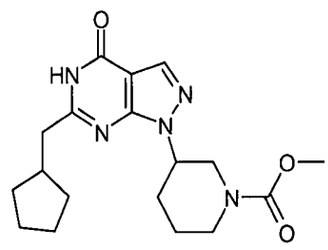

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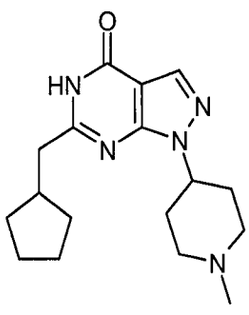

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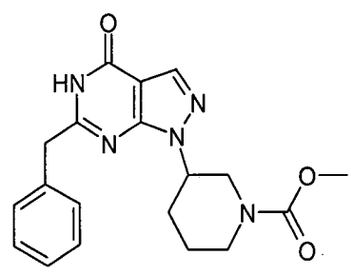

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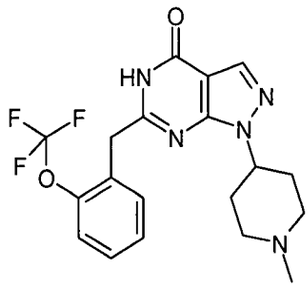

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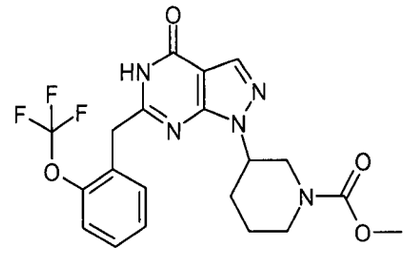

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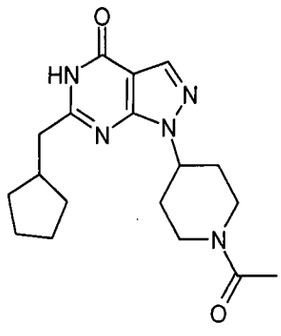

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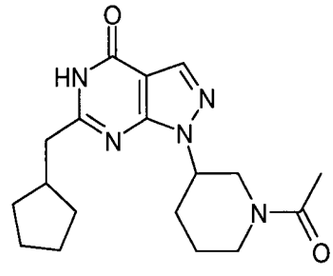

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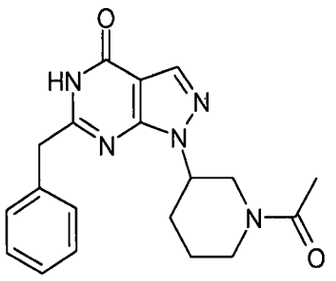
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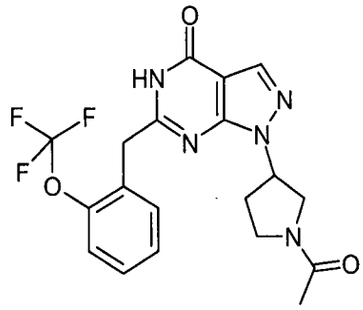
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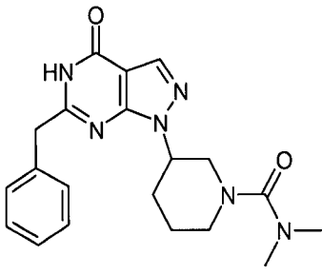
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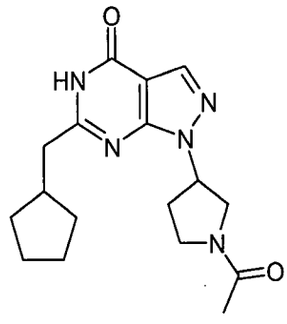
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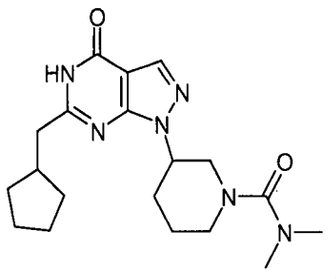
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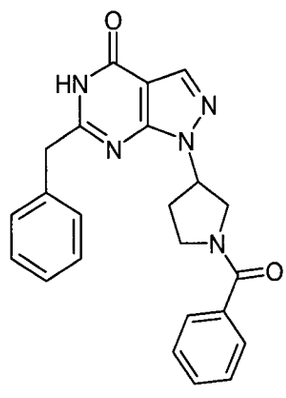
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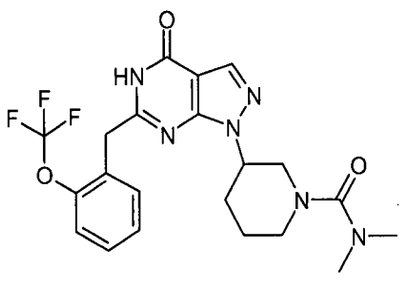
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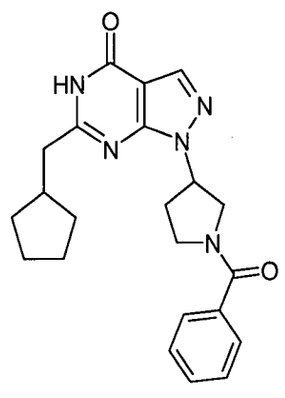
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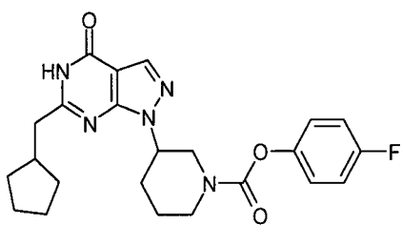
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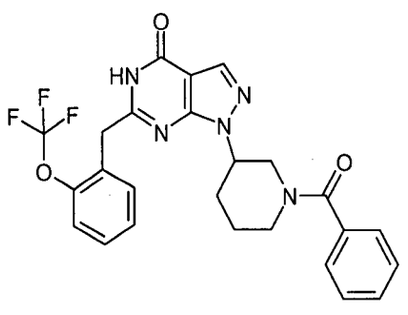
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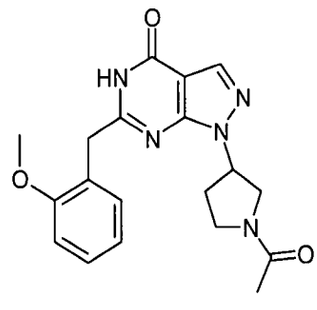
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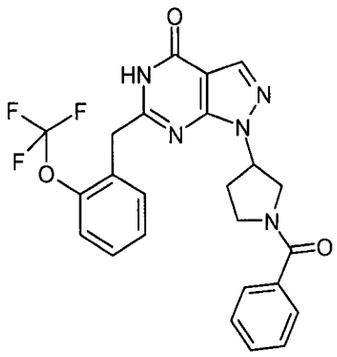

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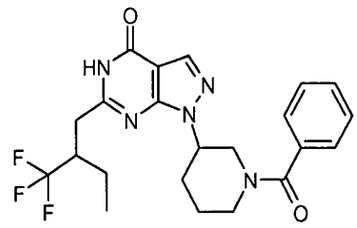

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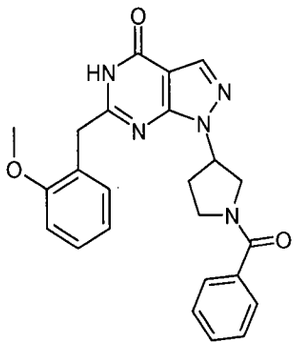

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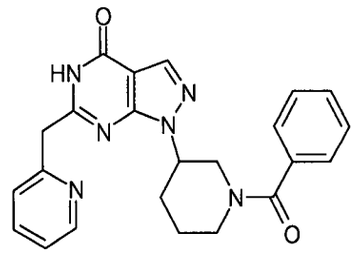

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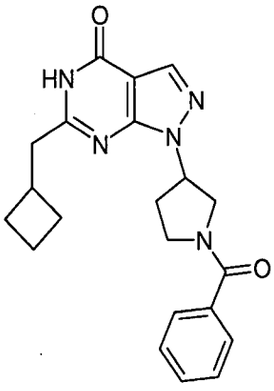

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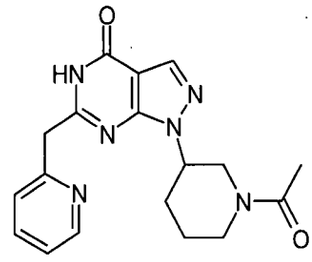

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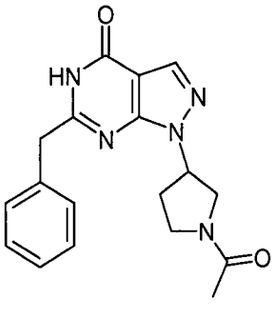

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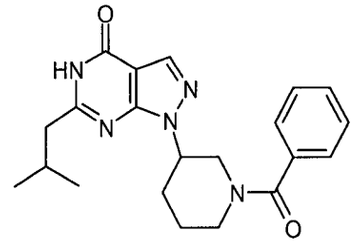

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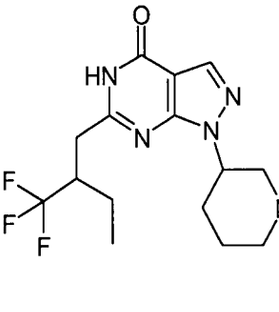

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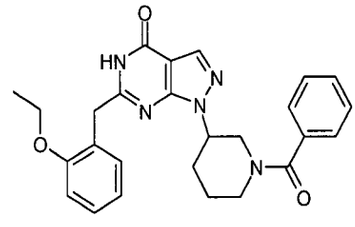

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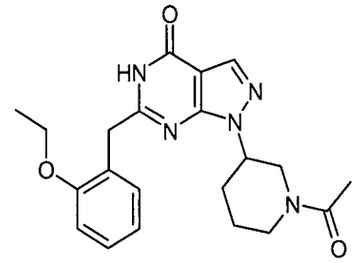

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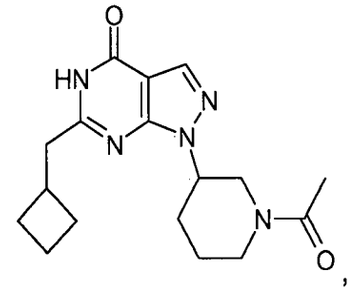

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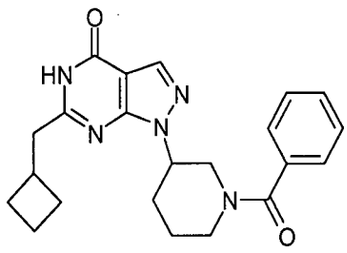

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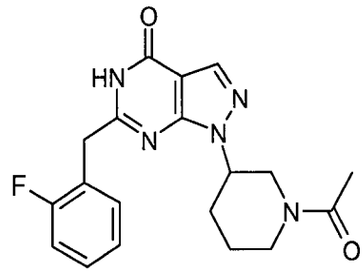

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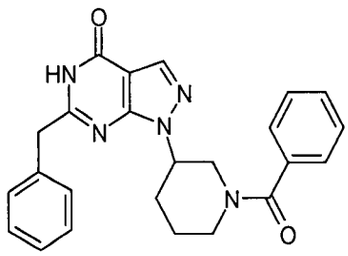

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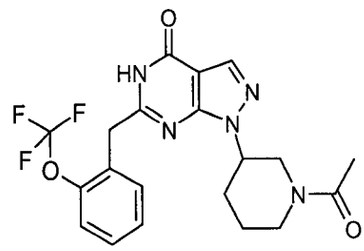

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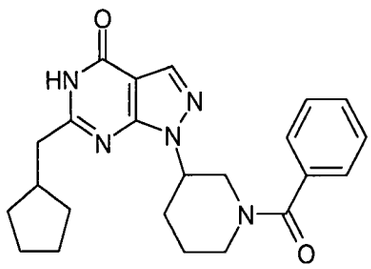

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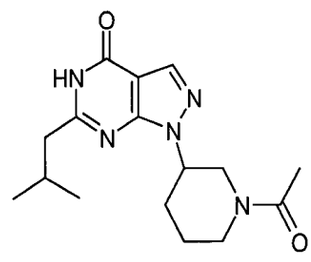

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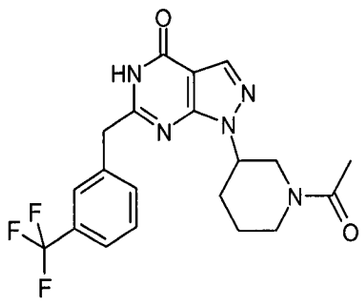

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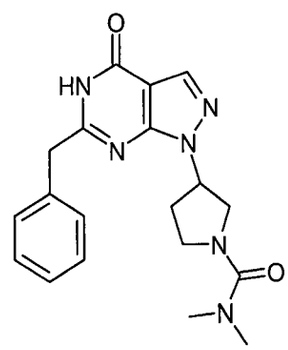

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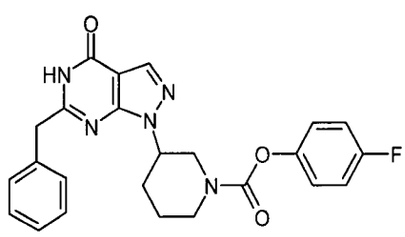

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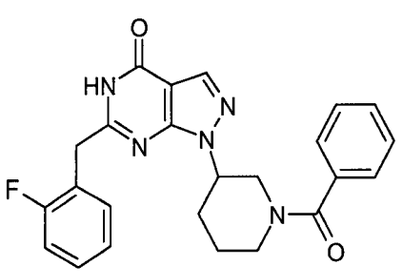

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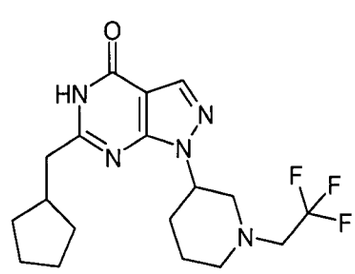

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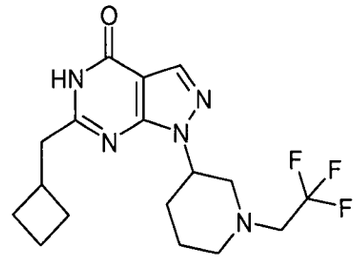

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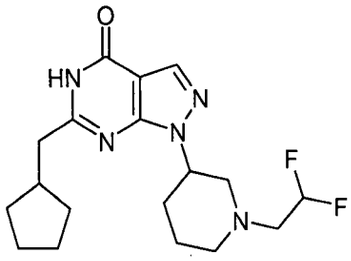
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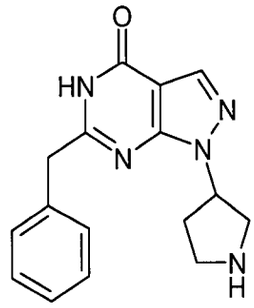
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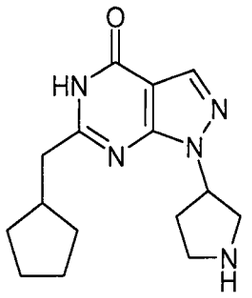
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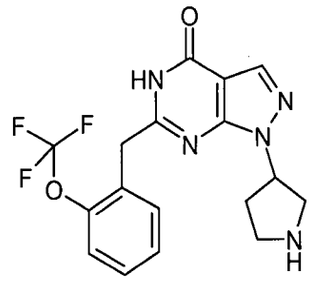
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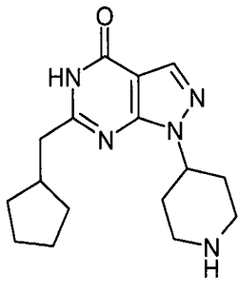
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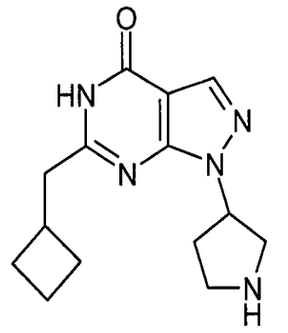
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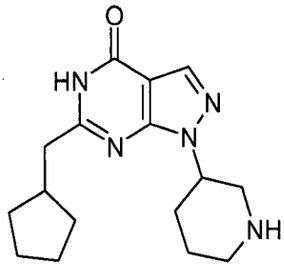
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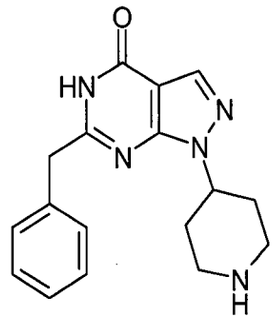
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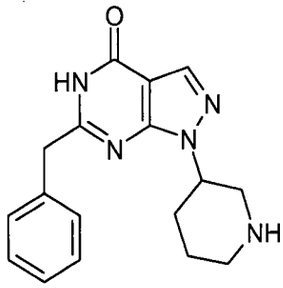
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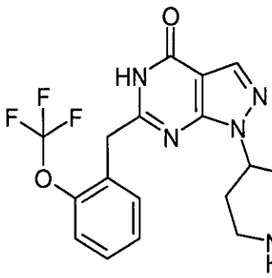
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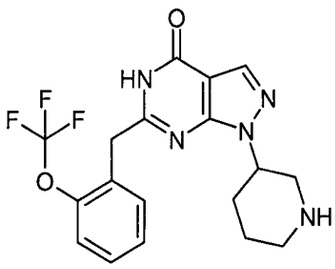
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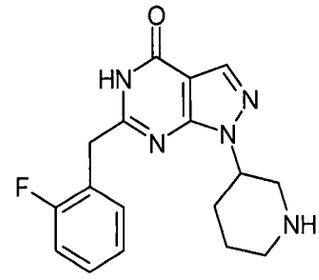
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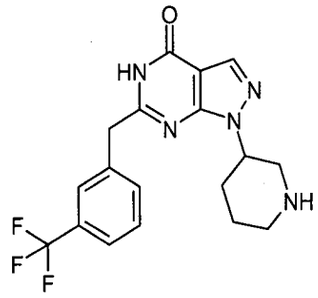

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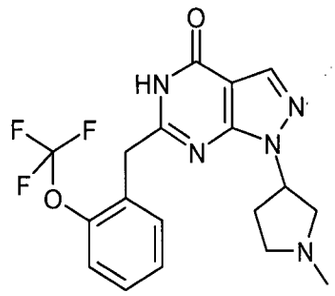

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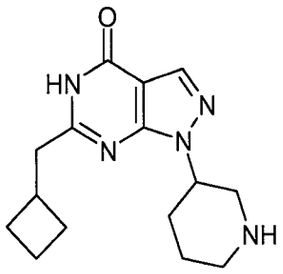

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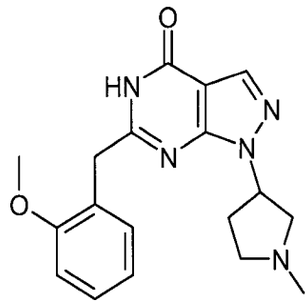

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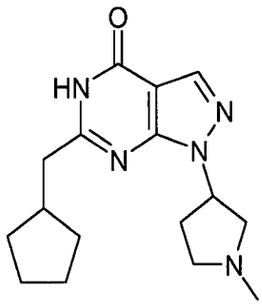

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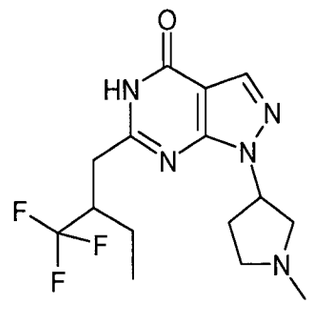

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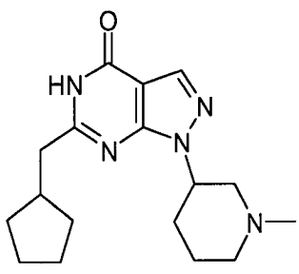

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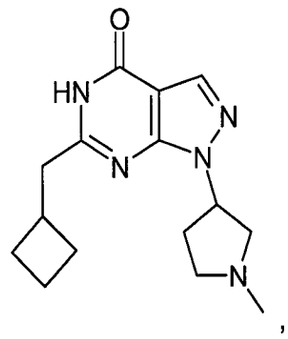

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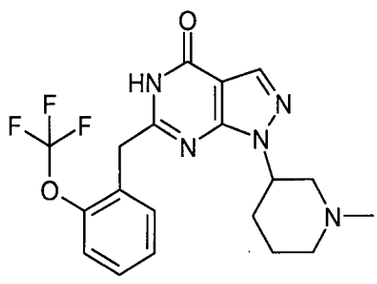

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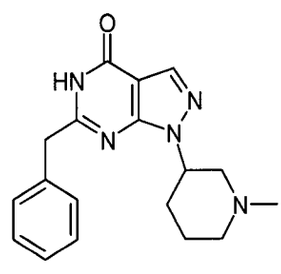

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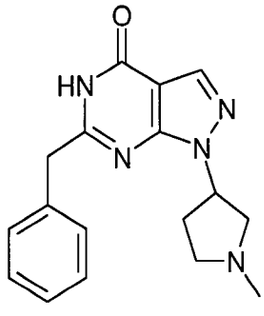

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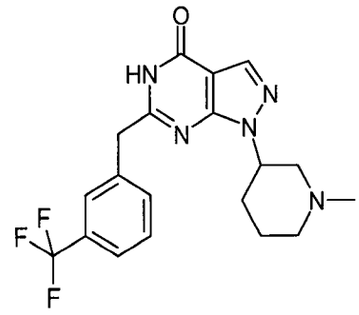

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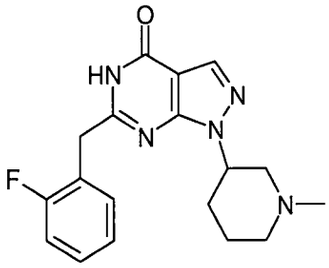

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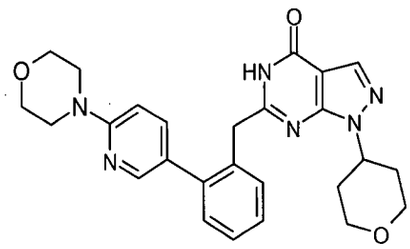

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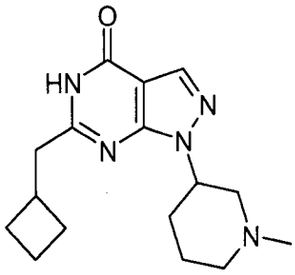

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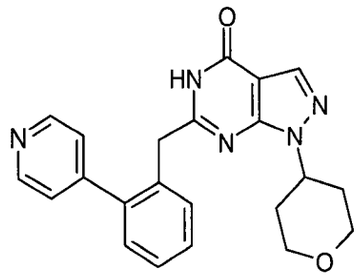

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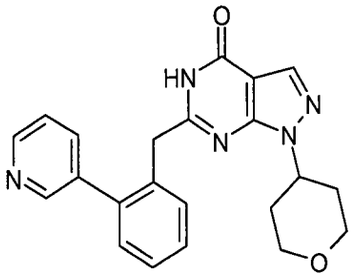

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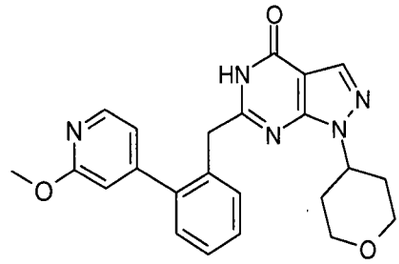

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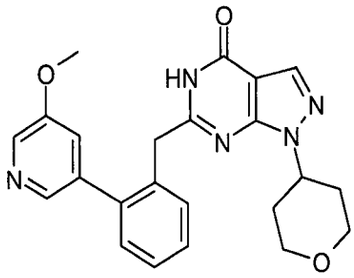

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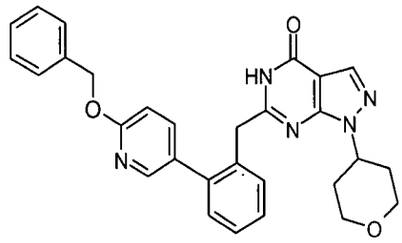

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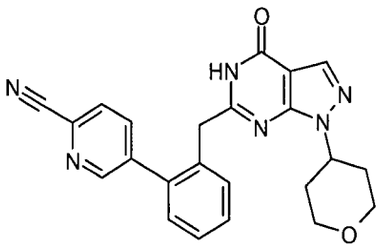

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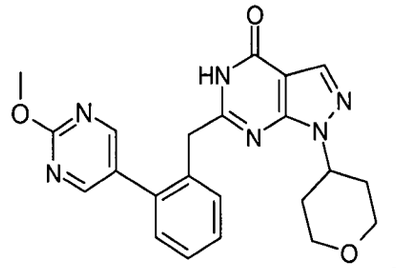

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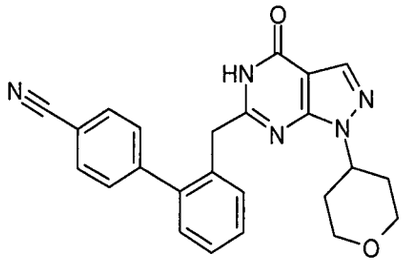

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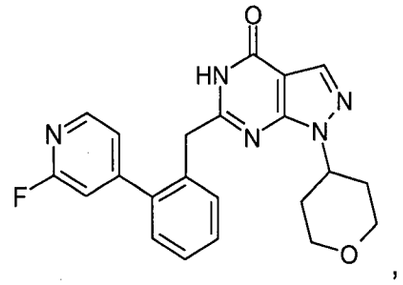

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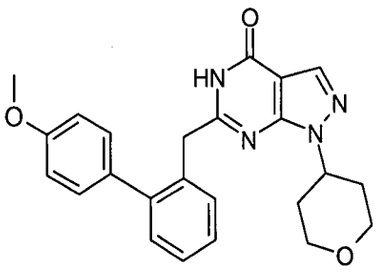
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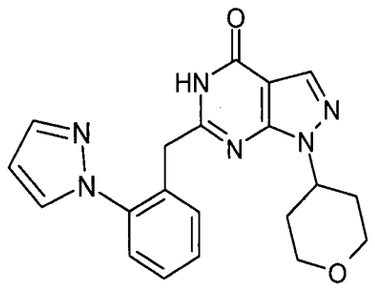
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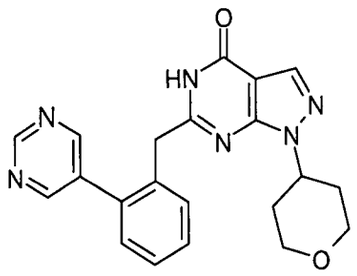
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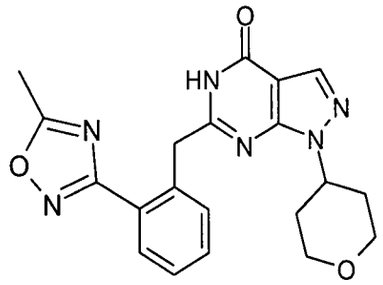
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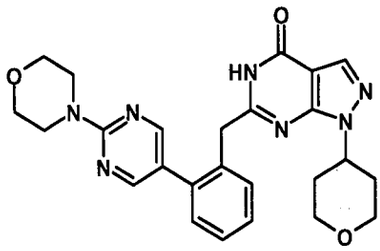
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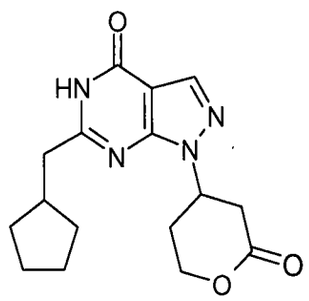
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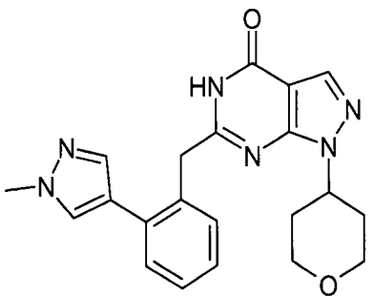
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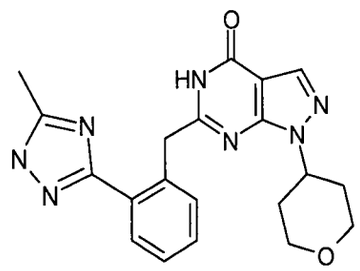
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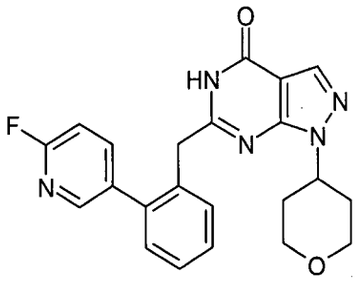
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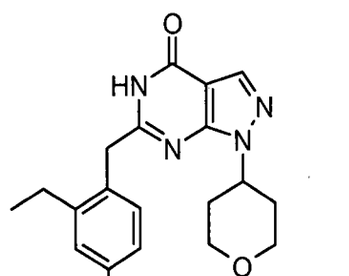
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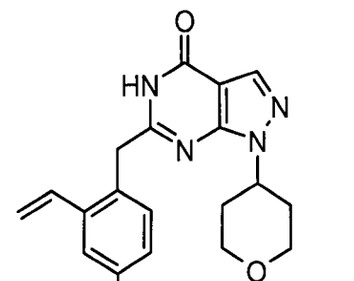
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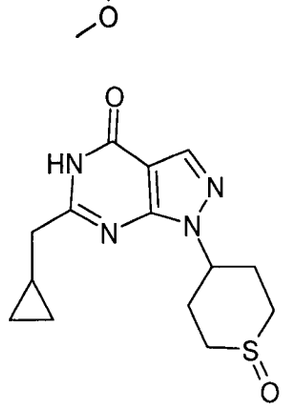
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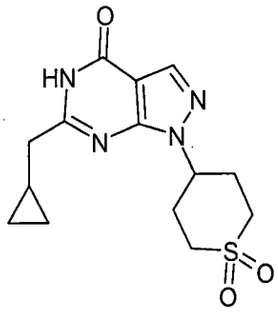

y los estereoisómeros de cada uno de ellos o los tautómeros de cada uno de ellos o los solvatos de cada uno de ellos o las sales farmacéuticamente aceptables de cada uno de ellos.

19. Un compuesto según cualquiera de las reivindicaciones 1 a 18, como un medicamento, preferiblemente como un medicamento para el tratamiento de una enfermedad del SNC, más preferiblemente como un medicamento para el tratamiento de una enfermedad del SNC, cuyo tratamiento es accesible mediante la inhibición de la PDE9.

20. El uso de un compuesto según las reivindicaciones 1 a 18, para la fabricación de un medicamento para el tratamiento de una enfermedad que es accesible mediante la inhibición de la PDE9.

21. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 18, para la fabricación de un medicamento para el tratamiento, alivio o prevención del deterioro cognitivo que está relacionado con la percepción, concentración, cognición, aprendizaje o memoria.

22. El uso según la reivindicación 21, caracterizado porque el medicamento es para el tratamiento, alivio o prevención de trastornos cognitivos que están relacionados con los deterioros del aprendizaje y de la memoria asociados con el envejecimiento, pérdidas de memoria asociadas con el envejecimiento, demencia vascular,

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traumatismo craneocerebral, ictus, demencia que aparece después de un ictus (demencia post-ictus), demencia post-traumática, deterioros de la concentración general, deterioros de la concentración en niños con problemas de aprendizaje y memoria, enfermedad de Alzheimer, demencia con cuerpos de Lewy, demencia con degeneración de los lóbulos frontales incluyendo el síndrome de Pick, enfermedad de Parkinson, parálisis nuclear progresiva, demencia con degeneración corticobasal, esclerosis lateral amiotrófica (ALS), enfermedad de Huntington, esclerosis múltiple, degeneración talámica, demencia de Creutzfeld-Jacob, demencia por VIH, esquizofrenia con demencia o psicosis de Korsakoff.

23. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 18, para la fabricación de un medicamento para el tratamiento de la enfermedad de Alzheimer.

24. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 18, para la fabricación de un medicamento para el tratamiento del deterioro cognitivo que es debido a la enfermedad de Alzheimer.

25. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 18, para la fabricación de un medicamento para el tratamiento de los trastornos del sueño, trastorno bipolar, síndrome metabólico, obesidad, diabetes mellitus, hiperglucemia, dislipidemia, deterioro de la tolerancia a la glucosa o una enfermedad de los testículos, cerebro, intestino delgado, músculo esquelético, corazón, pulmón, timo o bazo.

26. Una composición farmacéutica que comprende un compuesto según cualquiera de las reivindicaciones 1 a 18 y un vehículo farmacéutico.

27. Un método para el tratamiento de una enfermedad como se define en cualquiera de las reivindicaciones 19 a 25, en un paciente, que comprende administrar a dicho paciente una cantidad terapéuticamente activa de un compuesto según cualquiera de las reivindicaciones 1 a 18.

28. La combinación de un compuesto según cualquiera de las reivindicaciones 1 a 18, con otro agente activo para el tratamiento de la enfermedad de Alzheimer.

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Resumen

La invención se refiere a nuevas pirazolopirimidinonas disustituidas en 1,6, en las que i.) el átomo de nitrógeno del grupo pirazolo que está próximo al grupo pirimidino está unido a un heterociclo orgánico no aromático, que tiene al menos un heteroátomo en el anillo seleccionado entre O, N y S y ii.) al átomo de C entre los dos átomos de nitrógeno del anillo de pirimidinona está unido un segundo sustituyente mediante un puente de metileno opcionalmente sustituido. Según un aspecto de la invención los nuevos compuestos se destinan a la fabricación de medicamentos, en particular medicamentos para el tratamiento de trastornos relacionados con déficits en la percepción, concentración, aprendizaje o memoria. Los nuevos compuestos se destinan también a la fabricación de medicamentos para el tratamiento de la enfermedad de Alzheimer.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/053907

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/099210 A (BAYER HEALTHCARE AG [DE]; HENDRIX MARTIN [DE]; BAERFACKER LARS [DE]; E) 18 November 2004 (2004-11-18) cited in the application page 56 - page 57; claim 1 page 14, line 10 - page 15, line 9	1,2,14, 19-27
X	WO 2004/099211 A (BAYER HEALTHCARE AG [DE]; HENDRIX MARTIN [DE]; BAERFACKER LARS [DE]; E) 18 November 2004 (2004-11-18) page 79 - page 80; claim 1 page 17, line 6 - page 18, line 10	1,2,14, 19-27

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[X] Further documents are listed in the continuation of Box C.

[X] 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
26 May 2009	08/06/2009

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	Fink, Dieter

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/053907

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/018474 A (BAYER HEALTHCARE AG [DE]; HENDRIX MARTIN [DE]; BOESS FRANK-GERHARD [DE]) 4 March 2004 (2004-03-04) page 42; claim 1 page 17, line 1 - page 18, line 2	1-28
X	WO 2004/096811 A (PFIZER PROD INC [US]; BELL ANDREW SIMON [GB]; DENINNO MICHAEL PAUL [US]) 11 November 2004 (2004-11-11) cited in the application page 55 - page 56; claim 1	1,2,12, 19,20, 25-27
Y	page 55 - page 56; claim 1 page 59 - page 60; claims 5-8	1-28
A	WO 2004/026876 A (BAYER HEALTHCARE AG [DE]; HENDRIX MARTIN [DE]; BOESS FRANK-GERHARD [DE]) 1 April 2004 (2004-04-01) the whole document	1-28

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/053907

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004099210 A	18-11-2004	CA 2524898 A1	18-11-2004
		DE 10320785 A1	25-11-2004
		EP 1628980 A1	01-03-2006
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		EP 1626971 A1	22-02-2006
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		ES 2256797 T3	16-07-2006
		JP 2006503051 T	26-01-2006
		US 2006111372 A1	25-05-2006

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Industria y Comercio
SUPERINTENDENCIA

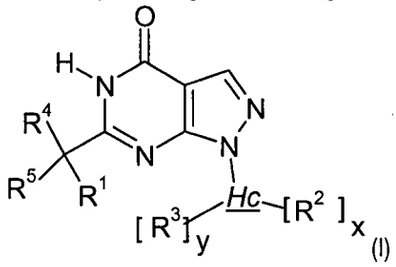
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:	(51) Int Cl: **C07D 487/004**
22) Fecha de solicitud:	(71)Solicitante(s) **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
(30) Prioridad (31) ***Prioridad*** **08153987.6** (32) ***Fecha*** **02/04/2008** (33) ***País*** **EP**	(72) Inventor(es) **RICCARDO GIOVANNINI Y OTROS**
	(74) Apoderado: **LUZ CLEMENCIA DE PAEZ**
(85) Fecha limite inicio fase nacional: 02/11/2010 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 01/04/2009 No. de solicitud PCT/EP2009/053907	(87) Publicación internacional Fecha: 08/10/2009 N° publicación: ***WO 2009/121919 A1***

(54) Titulo: **DERIVADOS DE 1-HETEROCICLILO-1,5-DIHIDRO-PIRAZOLO[3,4-D]PIRIMIDIN-4-ONA Y SU USO COMO MODULADORES DE LA PDE9A**

Reivindicación(es):

1. Un compuesto según la fórmula general I



(I)

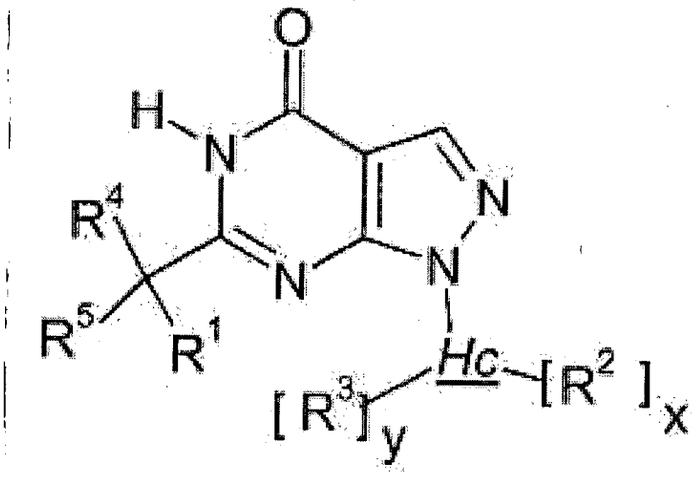
en la que

Hc es un grupo heterociclilo mono-, bi- o tricíclico, cuyos miembros del anillo son átomos de carbono y al menos 1, preferiblemente 1, 2 o 3, heteroátomos, que se seleccionan del grupo de nitrógeno, oxígeno y azufre, que está en la forma de $-S(O)_r$ - siendo r 0, 1 o 2, y

- dicho grupo heterociclilo es o comprende 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo y
- dicho grupo heterociclilo está unido a la estructura química (scaffold) por dicho 1 anillo monocíclico saturado, o parcialmente insaturado, no aromático, que comprende al menos 1 heteroátomo como miembro del anillo;

R^1 se selecciona del grupo de
alquil C_{1-8}-, alquenil C_{2-8}-, alquinil C_{2-8}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil C_{2-6}-, heterocicloalquil C_{3-7}-alquinil C_{2-6}-, arilo, aril-alquil C_{1-6}-, aril-alquenil C_{2-6}-, aril-alquinil C_{2-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-alquenil C_{2-6}-, y heteroaril-alquinil C_{2-6}-,
donde los miembros mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, yodo, oxo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, HO-alquil C_{1-6}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-O-, cicloalquil C_{3-7}-alquil C_{1-6}-O-, arilo, aril-alquil C_{1-6}-, heteroarilo, heteroaril-alquil C_{1-6}-, heteroaril-O-, heteroaril-alquil C_{1-6}-O-, piridin-2-ona unida por el N, piridin-2-ona-alquil C_{1-6}- unida por el N, piridin-2-ona-alquil C_{1-6}-O- unida por el N, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-O- estando el heterocicloalquilo C_{3-7} unido al O mediante uno de sus átomos C del anillo, heterocicloalquil C_{3-7}-alquil C_{1-6}-O- estando el heterocicloalquilo C_{3-7} unido al alquil C_{1-6}- mediante uno de sus átomos C del anillo, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-$(R^{10})N$-, R^{10}O-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y/o alquil C_{1-6}-SO_2-,
donde cualquiera de los grupos cicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-, arilo, heteroarilo, piridin-2-ona unida por el N, $(R^{10})_2N$-CO-alquil C_{1-6}- mencionados antes pueden estar opcionalmente sustituidos con uno o más sustituyentes, independientemente uno de otro, seleccionados del grupo que consiste en flúor, cloro, bromo, HO-, NC-, O_2N-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, F_3C-O-, HF_2C-O-, heterocicloalquil C_{3-7}-, R^{10}-O-alquil C_{1-6}-, R^{10}-S-alquil C_{1-6}-, alquil C_{1-6}-, $(R^{10})_2N$-, $(R^{10})_2N$-alquil C_{1-6}-, R^{10}-O-, R^{10}-S-, R^{10}-CO-, R^{10}O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-alquil C_{1-6}-, R^{10}-CO-$(R^{10})N$-, R^{10}-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-CO-O-, R^{10}O-CO-O-, R^{10}O-CO-O-alquil C_{1-6}-, R^{10}O-CO-$(R^{10})N$-, R^{10}O-CO-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-$(R^{10})N$-, $(R^{10})_2N$-SO_2-$(R^{10})N$-, $(R^{10})_2N$-CO-O-alquil C_{1-6}-, $(R^{10})_2N$-CO-$(R^{10})N$-alquil C_{1-6}-, R^{10}-SO_2-$(R^{10})N$-, R^{10}-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-$(R^{10})N$-alquil C_{1-6}-, $(R^{10})_2N$-SO_2-, $(R^{10})_2N$-SO_2-alquil C_{1-6}-, y/o alquil C_{1-6}-SO_2-;

R^2 independientemente de cualquier otro **R^2** se selecciona del grupo de:
H-, flúor, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, carboxi-, alquil C_{1-6}-, alquenil C_{2-6}-, alquinil C_{2-6}-, alquil C_{1-6}-S-, alquil C_{1-6}-S-alquil C_{1-3}-, preferiblemente alquil C_{1-6}-S-alquil C_{2-3}-, cicloalquil C_{3-7}-, cicloalquil C_{3-7}-alquil C_{1-6}-, cicloalquil C_{3-7}-alquenil C_{2-6}-, cicloalquil C_{3-7}-alquinil C_{2-6}-, heterocicloalquil C_{3-7}-, heterocicloalquil C_{3-7}-alquil C_{1-6}-, heterocicloalquil C_{3-7}-alquenil



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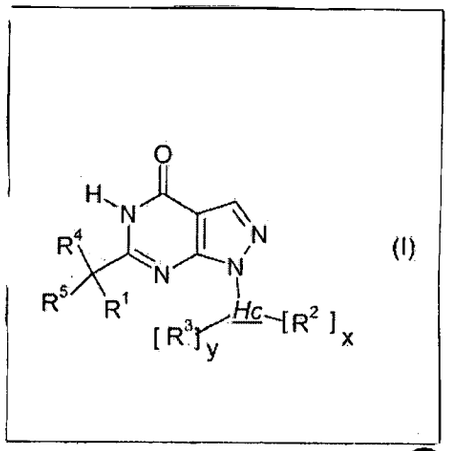
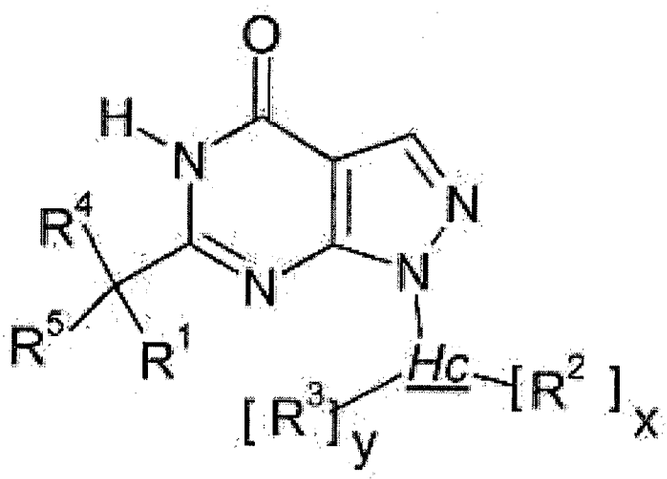


(I)



(I)

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 75,733
FECHA : SEPTIEMBRE 13 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-121065- -00000-0000
Fecha: 2010-09-30 11:37:47 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 723

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	156794820	13/09/2010	45,370,000.00

***** 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._____

CODO: 09255 - 841 - 351-5

723

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 78,499
FECHA : SEPTIEMBRE 20 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-121065- -00000-0000
Fecha: 2010-09-30 11:37:47 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 723

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	156798832	20/09/2010	42,239,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114	PTC CAP-II EXAMEN DE PATENTIBILID	470,000.00
			TOTAL : $	470,000.00

SON: CUATROCIENTOS SETENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

CdO: 09255 - 841 - 3515

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-121065- -00000-0000

Fecha: 2010-09-30 11:37:47 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 723

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

REFERENCIA	Radicación No.	10 121065
	Solicitud internacional	PCT/EP2009/053907
	Fecha inicio fase nacional	02/11/2010
	Trámite	11
	Evento	378
	Actuación	430.
	Oficio No.	

A 15747

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. A pesar de haber adjuntado el documento de cesión de manera coherente (numero y nombre de inventores al solicitante indicado), el titulo referido en dicho documento, no coincide con el presentado en el petitorio fase nacional:; por tal motivo se le requiere al solicitante para que aclare dicho punto.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 03 DIC. 2010
adpa11