CARLOS TAMAYO & ASOCIADOS
INTERNATIONAL PATENT AND TRADEMARK OFFICE

Trademark	Marcas
Patent	Patentes
Permit Health	Registro Sanitario
Software	Soporte Lógico
Commercial Name	Nombre Comercial
Design	Diseño

374

SUPERINTENDENCIA Y COMERCIO
Radicacion : 03027082 00000000
Fecha (AMD): 2003-06-09 14:24:43
Tramite : 811 PCT-PATENT 379 PAGE MAIL 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES
Folios: 1044

Señores
SUPERINTENDENCIA DE INDUSTRIA Y C
DIVISION DE NUEVAS CREACIONES
E. S. D.

REF: EXPEDIENTE: 03-027082
PATENTE PCT: "NUEVOS TIADIAZOLES Y OXADIAZOLES Y SU USO COMO INHIBIDORES DE FOSFODIESTERASA-7"

Estimados señores:

CARLOS ORLANDO MAYA RODRIGUEZ, mayor de edad, con domicilio y residencia en esta ciudad, identificado con la Cédula de Ciudadanía No.17.117.818 expedida en de Bogotá, Abogada en ejercicio, con Tarjeta Profesional No. 11.402 expedida por el Consejo Superior de la Judicatura, obrando en calidad de apoderada de la sociedad WARNER LAMBERT COMPANY LLC, según poder que obra dentro de las diligencias administrativas de la referencia, por medio de este escrito doy alcance a la patente PCT del asunto con el fin de anexar los siguientes documentos en ingles junto con su traducción al esañol:

- **Opinión escrita PCT regla 66 de los folios 3 a 19**
- **Notificación de recibo y listado de Oficinas Designadas de los Folios 20 a 24**
- **Notificación de información a las Oficinas Designadas, de los Folios 25 a 35**
- **Información a las Oficinas elegidas de los folios 31 a 35**
- **Información del Examen preliminar, primera opinión escrita de los Folios 36 a 116**
- **Publicación Internacional de los folios 117 a 553**
- **Reivindicaciones enmendadas de los folios 1554 a 649**

Carrera 7ª No. 17 - 51 Of. 710 Tels. (571) 341 9841
(571) 400 9180 (571) 286 8037 •Celular: (315) 317 1181
E-mail: trademarks1@tutopia.com • Bogotá, Colombia, S.A.
trademarks1@hotmail.com

CARLOS TAMAYO & ASOCIADOS
INTERNATIONAL PATENT AND TRADEMARK OFFICE

Trademark	Marcas
Patent	Patentes
Permit Health	Registro Sanitario
Software	Soporte Lógico
Commercial Name	Nombre Comercial
Design	Diseño

375

- **Notificación del número y fecha de la solicitud internacional, folios 650 a 706**

- **Respuesta a opinión escrita junto con dos pliegos de reivindicaciones enmendadas, Folios 707 a 850**

- **De la Autoridad del Examen Preliminar con sus anexos, de los folios 851 a 1045**

Ruego a usted tener en cuanta los documentos citados para los fines de rigor.

Atentamente,

CARLOS MAYA RODRÍGUEZ
C.C. 17.117.818 de Bogotá.
T.P. 17-402 del C .S .J

Carrera 7ª No. 17 - 51 Of. 710 Tels. (571) 341 9841
(571) 400 9180 (571) 286 8037 •Celular: (315) 317 1181
E-mail: trademarks1@tutopia.com • Bogotá, Colombia, S.A.
trademarks1@hotmail.com

PATENT COOPERATION TREATY

RECEIVED C
12 DEC 2002
Patents, Fresnes

PCT

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Hirsch, Denise
WARNER-LAMBERT COMPANY
c/o PARKE-DAVIS
Pfizer Global Research
& Development, Fresnes Laboratories
3-9 rue de la Loge, B.P. 100
F-94265 Fresnes
FRANCE

WRITTEN OPINION

(PCT Rule 66)

CONFIRMATION OF FAX 04-12.02

Date of mailing *(day/month/year)*	09.12.2002
Applicant's or agent's file reference: 018155-A305	REPLY DUE: within 0 month(s) and 15 days from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP01/11330	01/10/2001	02/10/2000

International Patent Classification (IPC) or both national classification and IPC

C07D285/135

Applicant

WARNER-LAMBERT COMPANY

1. This written opinion is the second drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 02/02/2003.

Name and mailing address of the international preliminary examining authority:
European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Paya Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized officer / Examiner
Allard, M

Formalities officer (incl. extension of time limits)
Smith, K
Telephone No. +31 70 340 3479

00399 327

WRITTEN OPINION International application No. PCT/EP01/11330

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

   Description, pages:

   1-200 as originally filed

   Claims, No.:

   1-31 as received on 29/10/2002 with letter of 25/10/2002

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing: .

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 20-22,

because:

   ☒ the said international application, or the said claims Nos. 20-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-5, 7-9, 13, 31
Inventive step (IS)	Claims	1-5, 7-9, 13, 31
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

Reference is made to the following document:

D1: DD 251 979 A (PÄDAGOGISCHE HOCHSCHULE 'DR. THEODOR NEUBAUER', ERFURT/MÜHLHAUSEN) 2 December 1987 (1987-12-02)

Re Item III

N n-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step r industrial applicability; citations and explanations supporting such statement

Novelty (Article 33(2) PCT)

Claims 1-5, 7-9, 13 and 31 lack novelty in the light of the disclosure of D1. It would appear from your reply of 25.10.2002 that the content of D1, particularly the formula of the disclosed compounds, has been misinterpreted, leading to an inappropriate disclaimer (note for instance that example 1 of D1 is not disclaimed).

Inventive step (Article 33(3) PCT)

Claims 1-5, 7-9,13 and 31, which lack novelty, cannot involve an inventive step.

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Recibido. 12 de diciembre de 2002. Patentes. Fresnes

TRATADO DE COOPERACION EN MATERIA DE PATENTES

De: Autoridad de Examen Preliminar Internacional

A: Hirsch, Denise

WARNER-LAMBERT COMPANY

c/o PARKE-DAVIS

Pfizer Global Research & Development, Fresnes Laboratories

3-9 rue de la Loge, B.P. 100

F-94265 Fresnes

FRANCIA

PCT

OPINION ESCRITA

(Reglamentación PCT 66)

Confirmación del fax del 4-12-02

Fecha de envío por correo (día/mes/año): 09-12-2002

Referencia del solicitante o agente: 018155-A305.

VENCIMIENTO DE LA RESPUESTA: dentro de 0 mes(es) y 15 días desde la fecha de envío por correo antes mencionada

Solicitud internacional N° PCT/EP01/11330

Fecha de presentación internacional (día/mes/año): 01/10/2001

Fecha de prioridad (día/mes/año): 02/10/2000

Clasificación Internacional de Patentes (IPC) o tanto clasificación nacional como IPC: C07D285/135.

Solicitante: WARNER-LAMBERT COMPANY

1. La presente opinión escrita es la segunda emitida por esta Autoridad de Examen Preliminar Internacional.
2. Esta opinión contiene indicaciones relacionadas con los siguientes puntos:

I. ☒ Base de la opinión

II. ☐ Prioridad

III. ☒ No formulación de una opinión sobre la novedad, actividad inventiva y aplicación industrial

IV. ☐ Falta de unidad de la invención

V. ☒ Declaración razonada conforme a la reglamentación 66.2(a)(ii) con respecto a la novedad, actividad inventiva o aplicación industrial; citaciones y explicaciones que respaldan dicha declaración

VI. ☐ Ciertos documentos citados

VII. ☐ Ciertos defectos en la solicitud internacional

VIII. ☐ Ciertas observaciones sobre la solicitud internacional

3. Por el presente se pide al solicitante a que responda esta opinión.

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¿Cuándo? Ver el plazo indicado anteriormente. El solicitante puede, antes del vencimiento de ese plazo, solicitar a esta Autoridad, el otorgamiento de una extensión de plazo, ver Reglamentación 66.2(d).

¿Cómo? Presentando una respuesta por escrito, acompañada, si fuera adecuado, por modificaciones, conforme a la Reglamentación 66.3. Sobre el formulario e idioma de las modificaciones, ver las Reglamentaciones 66.8 y 66.9.

Además: Por una oportunidad adicional para presentar modificaciones, ver la Reglamentación 66.4.
Por la obligación del examinador de considerar las modificaciones y/o argumentos, ver la Reglamentación 66.4bis.
Por una comunicación informal con el Examinador, ver la Reglamentación 66.6.

Si no se presenta una respuesta, el informe de examen preliminar internacional se establecerá en base a esta opinión.

4. La fecha final en la cual debe establecerse el informe de examen preliminar internacional conforme a la Reglamentación 69.2 es: 02/02/2003.

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Nombre y domicilio postal de la Autoridad de Examen Preliminar Internacional:

Oficina de Patentes Europea - P.B. 5818 Patentlaan 2, NL-2280 HV Rijswijk - (expresión en otro idioma)

Tel: +31 70 340-2040. Tx: 31 651 epo nl

Fax: +31 70 340-3016

Funcionario autorizado: Allard, M. (sello en otro idioma)

Funcionario sobre formalidades (incluyendo extensiones de plazo): Smith, K.

Teléfono No. +31 70 340-3479

Formulario PCT/IPEA/408 (cubierta)(enero de 1994)

OPINIÓN ESCRITA

Solicitud Internacional No **PCT/EP01/11330**

I. Base de la opinión

1. Con respecto a los **elementos** de la solicitud internacional (las Páginas de reemplazo que han sido presentadas ante la Oficina Receptora en respuesta a un pedido conforme al artículo 14 se mencionan en esta opinión como "originalmente presentadas"):

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Memoria descriptiva, páginas:

1-200 tal como se presentaron originalmente

Reivindicaciones, No.:

1-31 tal como fueron recibidas el 29/10/2002 con la carta del 25/10/2002

2. Con respecto al **idioma**, todos los elementos marcados anteriormente estuvieron disponibles o fueron presentados ante esta Autoridad en el idioma en el cual se presentó la solicitud internacional, a menos que se indique lo contrario en este punto.

Estos elementos estuvieron disponibles o fueron presentados ante esta Autoridad en el siguiente idioma: , que es:

☐ el idioma de una traducción proporcionada para los fines de la búsqueda internacional (conforme a la reglamentación 23.1(b)).

☐ el idioma de la publicación de la solicitud internacional (conforme a la reglamentación 48.3(b)).

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☐ el idioma de una traducción proporcionada para los fines del examen preliminar internacional (conforme a la reglamentación 55.2 y/o 55.3).

3. Con respecto a cualquier **secuencia de nucleótidos y/o aminoácidos** divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo en base al listado de secuencias:

☐ contenido en la solicitud internacional en forma escrita.

☐ presentado junto con la solicitud internacional de forma legible mediante computadora.

☐ presentado con posterioridad ante esta Autoridad en forma escrita.

☐ presentado con posterioridad ante esta Autoridad en forma legible mediante computadora.

☐ Se ha presentado la declaración de que el listado de secuencias escrito presentado posteriormente no excede la divulgación de la solicitud internacional tal como fue presentada.

☐ Se ha presentado la declaración de que la información registrada en forma legible mediante computadora es idéntica al listado de secuencias escrito.

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4. Las modificaciones tuvieron como resultado la cancelación de:

☐ la memoria descriptiva, páginas:

☐ las reivindicaciones, Nos:

☐ los dibujos, láminas:

Formulario PCT/IPEA/408 (casilleros I-VIII, página 1)(julio de 1998)

OPINIÓN ESCRITA

Solicitud Internacional No **PCT/EP01/11330**

5. ☐ Este informe ha sido establecido como si (alguna de) las modificaciones no hubieran sido realizadas debido a que se ha considerado que exceden lo divulgado tal como fue presentado (reglamentación 70.2(c)):

(Cualquier página de reemplazo que contenga dichas modificaciones be ser referida conforme al punto 1 y adjuntada a este informe)

6. Observaciones adicionales, si fueran necesarias:

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III. No establecimiento de una opinión sobre la novedad, actividad inventiva y aplicación industrial

1. Los temas sobre si la invención reivindicada es novedosa, si implica actividad inventiva (ser no obvia) o si tiene aplicación industrial no han sido y no serán examinados con respecto a:

☐ la solicitud internacional completa,

☒ reivindicaciones Nos. 20-22,

debido a:

☒ dicha solicitud internacional o dichas reivindicaciones 20-22 se refieren a un tema que no requiere de un examen preliminar internacional *(especificar):*

ver página por separado

☐ la memoria descriptiva, reivindicaciones y dibujos (indicar elementos particulares más abajo) o dichas reivindicaciones Nos. son tan poco claras que no puede formarse ninguna opinión significativa al respecto *(especificar):*

☐ las reivindicaciones o dichas reivindicaciones Nos. están respaldadas de forma tan inadecuada por la memoria descriptiva que no puede formarse ninguna opinión significativa al respecto.

☐ no se ha establecido ningún informe de búsqueda internacional para dichas reivindicaciones Nos..

2. No puede emitirse una opinión escrita debido a que el listado de secuencias de nucleótidos o aminoácidos no cumple con los patrones proporcionados en el Anexo C de las Instrucciones Administrativas:

☐ se ha presentado la forma escrita o no cumple con el patrón.

☐ la forma legible mediante computadora no ha sido presentada o no cumple con el patrón.

V. Declaración razonada conforme a la Reglamentación 66.2(a)(ii) con respecto a la novedad, actividad inventiva o aplicación industrial; citaciones y explicaciones que respaldan dicha declaración

1. Declaración

Novedad (N)	reivindicaciones 1-5, 7-9, 13, 31
Actividad inventiva (IS)	reivindicaciones 1-5, 7-9, 13, 31
Aplicación Industrial (IA)	reivindicaciones

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Formulario PCT/IPEA/408 (casilleros I-VIII, página 2)(julio de 1998)

OPINIÓN ESCRITA

Solicitud Internacional No **PCT/EP01/11330**

2. Citaciones y explicaciones

ver página por separado

Formulario PCT/IPEA/408 (casilleros I-VIII, página 3)(julio de 1998)

OPINIÓN ESCRITA

PAGINA POR SEPARADO

Solicitud Internacional No **PCT/EP01/11330**

Se hace referencia al siguiente documento:

. 004/13 391

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D1: DD 251 979A (PÄDAGOGISCHE HOCHSCHULE 'DR. THEODOR NEUBAUER', ERFURT/MÜHLHAUSEN) 2 de diciembre de 1987 (02-12-1987)

Ref. Punto III

No establecimiento de una opinión sobre la novedad, actividad inventiva y aplicación industrial

Las reivindicaciones 20-22 se refieren a un tema que esta Autoridad considera como cubierto por las disposiciones de la Reglamentación 67.1(iv) del PCT. Como consecuencia, no se formulará opinión alguna sobre la aplicación industrial del objeto de estas reivindicaciones (artículo 34(4)(a)(I) PCT).

Ref. Punto V

Declaración razonada conforme a la reglamentación 66.2(a)(ii) sobre la novedad, actividad inventiva o aplicación industrial; citaciones y explicaciones que respaldan dicha declaración

Novedad (artículo 33(2) PCT)

Las reivindicaciones 1-5, 7-9, 13 y 31 carecen de novedad en vistas de la divulgación de D1. De su respuesta del 25-10-2002 parecería que el contenido de D1, particularmente la fórmula de los compuestos divulgados, ha sido mal interpretada,

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llevando una renuncia inadecuada (ver, por ejemplo, que el ejemplo 1 de D1 no ha sido rechazado).

Actividad inventiva (artículo 33(3) PCT)

Las reivindicaciones 1-5, 7-9, 13 y 31 que carecen de novedad no pueden implicar actividad inventiva.

PCT/EP01/11330

PATENT COOPERATION TREATY

RECEIVED IN
- 6. NOV. 2001
PCT
Patents. Fresnes

From the INTERNATIONAL BUREAU

To:

HIRSCH, Denise
Warner-Lambert Company
c/o Parke-Davis
Pfizer Global Research & Development
Fresnes Laboratories, 3-9 rue de la Loge
F-94265 Fresnes
FRANCE

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
29 October 2001 (29.10.01)	
Applicant's or agent's file reference	**International application No.**
018215-A305	PCT/EP01/11330

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

WARNER-LAMBERT COMPANY (for all designated States except US)
VERGNE, Fabrice et al (for US)

International filing date	:	01 October 2001 (01.10.01)
Priority date(s) claimed	:	02 October 2000 (02.10.00)
Date of receipt of the record copy by the International Bureau	:	12 October 2001 (12.10.01)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ, EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU, LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ, UA,UG,US,UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [ ] confirmation of precautionary designations
- [X] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Jean-Marie MCADAMS

Telephone No. (41-22) 338.83.38

00426 394

PCT/EP01/11330

TRATADO DE COOPERACION EN MATERIA DE PATENTES

[Aparece un sello que reza:] Recibido el 6 de noviembre de 2001. Patentes. Fresnes.

De la Oficina Internacional

A: HIRSCH, Denise

Warner-Lambert Company

c/o PARKE-DAVIS

Pfizer Global Research & Development, Fresnes Laboratories

3-9 rue de la Loge

F-94265 Fresnes

FRANCIA

PCT

NOTIFICACION DEL RECIBO DE LA COPIA DE REGISTRO

(Reglamentación PCT 24.2(a))

Fecha de envío por correo (día/mes/año): 29 de octubre de 2001 (29-10-01)

Referencia del solicitante o agente: ~~018315~~-018155-A305.

NOTIFICACION IMPORTANTE

Solicitud internacional N° PCT/EP01/11330

Por el presente, se notifica al solicitante que la Oficina Internacional ha recibido la copia de registro de la solicitud internacional según se detalla a continuación.

Nombre(s) del(los) solicitante(s) y Estado(s) por/en los cuales son solicitantes:
WARNER-LAMBERT COMPANY (para todos los Estados designados excepto los Estados Unidos de Norteamérica)
VERGNE, Fabrice et al (para los Estados Unidos de Norteamérica)

Fecha de presentación internacional: 01 de octubre de 2001 (01-10-01)
Fecha(s) de prioridad reivindicada(s): 02 de octubre de 2000 (02-10-00)
Fecha de recibo de la copia de registro por la Oficina Internacional: 12 de octubre de 2001 (12-10-01)

Listado de Oficinas designadas:
AP: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW
EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
EP: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

Nacional: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

ATENCION:

El solicitante debería controlar cuidadosamente la información que aparece en esta Notificación. En caso de observarse discrepancias entre estos datos y las indicaciones de la solicitud internacional, el solicitante debería informar inmediatamente a la Oficina Internacional.

Además, se dirige la atención del solicitante a la información contenida en el Anexo, relacionada con:

[X] límites de tiempo para entrar en la fase nacional

[ ] confirmación de designaciones preventivas

[X] requisitos relacionados con los documentos de prioridad

Se envía una copia de esta Notificación a la Oficina Receptora y a la Autoridad de Búsqueda Internacional.

Oficina Internacional de WIPO.

34, chemin des Colombettes, 1211 Geneva 20, Suiza.

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004193

Fax N° (41-22) 740.14.35

Funcionario autorizado: Jean-Marie MCADAMS [firma ilegible]

Teléfono N° (41-22) 338.83.38

Formulario PCT/IB/301 (abril de 2000)

004406845.

RECEIVED ON
19. APR. 2002
Patents Fresnes

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:
HIRSCH, Denise
Warner-Lambert Company
c/o Parke-Davis
Pfizer Global Research & Development
Fresnes Laboratories, 3-9 rue de la Loge
F-94265 Fresnes
FRANCE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year)	
11 April 2002 (11.04.02)	
Applicant's or agent's file reference	**IMPORTANT NOTICE**
018155-A305	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP01/11330	01 October 2001 (01.10.01)	02 October 2000 (02.10.00)

Applicant
WARNER-LAMBERT COMPANY et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:
   KP,KR,US
   In accordance with Rule 47.1(a), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EA,EC, EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA, MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OA,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on
   11 April 2002 (11.04.02) under No. WO 02/28847

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into national phase
   The applicable time limit for entering the national phase will, subject to what is said in the following paragraph be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article22(1) as modified with effect from 1 April 2002 applies in respect of the designated Office. For further details, see PCT Gazette No.44/2001 of 1 November 2001, pages 18928, 18932 and 18934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.
   In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20,21,30 or 31 months , or other time limit), Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.
   For filing a demand for international preliminary examination, see the PCT Applicant's Guide, Volume I/A, Chapter IX. Only an an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II.)
   It is the applicant's sole responsibility to monitor all these limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.81.11

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WO 02/28847

PCT/EP01/11330

[SELLO] RECIBIDO EL 19 DE ABRIL DE 2002, Patentes, Fresnes

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

NOTIFICACION PARA INFORMAR AL SOLICITANTE SOBRE LA COMUNICACION DE LA SOLICITUD INTERNACIONAL A LAS OFICINAS DESIGNADAS

(Norma PCT 47.1(c), primera oración)

De la OFICINA INTERNACIONAL

A: HIRSCH, Denise

Warner-Lambert Company, c/o Parke-Davis, Pfizer Global Research & Development, Fresnes Laboratories, 3-9 rue de la Loge, F-94265 Fresnes, FRANCIA

Fecha de envío (día, mes, año): 11 de abril de 2002 (11.04.02)

Referencia de archivo del Solicitante o Agente: 018155-A305

NOTIFICACIÓN IMPORTANTE

Solicitud Internacional No. PCT/EP01/11330

00422

Fecha de presentación internacional (día, mes, año): 01 de octubre de 2001 (01.10.01)
Fecha de Prioridad (día, mes, año): 02 de octubre de 2000 (02.10.00)

Solicitante: **WARNER-LAMBERT COMPANY y otros**

1. Por la presente se notifica que la Oficina Internacional ha comunicado, conforme al Art.20, la solicitud internacional a las siguientes oficinas designadas en la fecha indicada más arriba como la fecha de envío de esta notificación: KP, KR, US

Conforme a la Norma 47.1(c), tercera oración, cada Oficina designada aceptará esta notificación como prueba definitiva de que la comunicación de la solicitud internacional se ha realizado debidamente en la fecha de envío indicada más arriba y que no es necesario que el solicitante presente copia de la solicitud internacional ante las Oficinas designadas.

2. Las siguientes Oficinas designadas han renunciado al requisito de dicha comunicación en esta fecha:
AE,AG,AL,AM,AP,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,
DE,DK,DM,DZ,EA,EC,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,

JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ, OA,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA

La comunicación se remitirá a esas Oficinas sólo a su pedido. Más aún, esas Oficinas no exigen al solicitante que presente copia de la solicitud internacional (Norma 49.1(a-bis)).

3. Se adjunta a esta notificación, copia de la solicitud internacional publicada por la Oficina Internacional el 11 de abril de 2002 (11.04.02) como WO 02/28847

4. PLAZOS para presentar un pedido de examen preliminar internacional y para ingresar en fase nacional

El plazo aplicable para ingresar en fase nacional será, en virtud de lo indicado en el párrafo siguiente, de 30 MESES desde la fecha de prioridad, no sólo con respecto a cualquier oficina elegida si se presenta un pedido para el examen preliminar internacional antes del vencimiento de los 19 meses desde la fecha de prioridad, sino también con respecto a cualquier oficina designada en ausencia de la presentación de dicho pedido, en el que se aplica la sección 22(1) tal como fue modificado y con vigencia desde el 1 de abril de 2002 con

respecto a la oficina designada. Para más detalles, véase el Diario de PCT No. 44/2001 del 1 de noviembre de 2001, páginas 19926, 19932 y 19934, así como también las Novedades de PCT, ediciones de octubre y noviembre de 2001 y febrero de 2002.

En la práctica, se continuarán aplicando los plazos que no sean el de 30 meses para varios períodos de tiempo con respecto a ciertas oficinas designadas o elegidas. Para actualizaciones regulares sobre los plazos aplicables (20,21,30 o 31 meses, u otro plazo) de cada oficina, referirse al Diario de PCT, a las Novedades de PCT y a la Guía del Solicitante de PCT, Volumen II, Capítulos Nacionales, los cuales se encuentran disponibles en el sitio de internet de la OMPI en **http://www.wipo.int/pct/en/index.html**.

Para la presentación de un pedido de examen preliminar internacional, véase la Guía del Solicitante de PCT, Volumen I/A, Capítulo IX. Sólo un solicitante nativo o que tiene domicilio en un Estado Firmante de PCT que se rige por el Capítulo II tiene el derecho de presentar un pedido de examen preliminar internacional (en este momento, todos los estados firmantes del PCT están obligados por el Capítulo II).

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El control de todos estos plazos es de responsabilidad exclusiva del solicitante.

La Oficina Internacional de WIPO, 34, chemin des Colombettes, 1211 Ginebra 20, Suiza.

Fax: (41-22)740.14.35.

Funcionario Autorizado: J. Zahra. Tel. (41-22)338.91.11

Formulario PCT/IB/308 (abril de 2002)

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RECEIVED ON
18.NOV.2002
Patents. Fresnes

PATENT COOPERATION TREATY

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PCT

From the INTERNATIONAL BUREAU

To:

HIRSCH, Denise
Warner-Lambert Company
c/o Parke-Davis
Pfizer Global Research & Development
Fresnes Laboratories, 3-9 rue de la Loge
F-94265 Fresnes
France

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year)	
13 November 2002 (13.11.02)	
Applicant's or agent's file reference	**IMPORTANT INFORMATION**
018155-A305 TP	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP01/11330	01 October 2001 (01.10.01)	02 October 2000 (02.10.00)

Applicant
WARNER-LAMBERT COMPANY et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
   National :AU,BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW
   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
   National :AE,AG,AL,AM,AT,AZ,BA,BB,BR,BY,BZ,CH,CO,CR,CU,CZ,DK,DM,DZ,EC,EE, ES,FI,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG, MK,MW,MX,MZ,NZ,PH,PT,SD,SE,SG,SI,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Farid ABBOU

Telephone No. (41-22) 338.83.38

0042405

PCT/EP01/11330

TRATADO DE COOPERACION EN MATERIA DE PATENTES

[Aparece un sello que reza:] Recibido el 18 de noviembre de 2002. Patentes. Fresnes.

De la Oficina Internacional

A: HIRSCH, Denise

Warner-Lambert Company

c/o PARKE-DAVIS

Pfizer Global Research & Development, Fresnes Laboratories

3-9 rue de la Loge

F-94265 Fresnes

FRANCIA

PCT

INFORMACIÓN REFERIDA A LAS OFICINAS ELEGIDAS NOTIFICADAS SOBRE SU ELECCIÓN

(Reglamentación PCT 61.3)

Fecha de envío por correo (día/mes/año): 13 de noviembre de 2002 (13-11-02)

Referencia del solicitante o agente: 018155-A305. TP

NOTIFICACION IMPORTANTE

Solicitud internacional N° PCT/EP01/11330

Fecha de presentación internacional (día/mes/año): 01 de octubre de 2001 (01-10-01)
Fecha de prioridad (día/mes/año): 02 de octubre de 2000 (02-10-00)
Solicitante: **WARNER-LAMBERT COMPANY**

1. Por el presente se informa al solicitante que, conforme al artículo 31(7), la Oficina Internacional ha notificado a cada una de las siguientes oficinas sobre su elección:

EP: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
Nacional: AU, BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. Las siguientes Oficinas han renunciado al requisito de notificación sobre su elección; la notificación les será enviada por la Oficina Internacional sólo si lo solicitan:

AP: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW
EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
Nacional: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH,

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GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NZ, PH, PT, SD, SE, SG, SI, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

3. Se recuerda al solicitante que debe ingresar en la "fase nacional" **antes del vencimiento de los 30 meses desde la fecha de la prioridad** en cada una de las Oficinas anteriormente indicadas. Esto debe hacerse abonando la(s) tasa(s) nacional(es) y presentando, si estuviera prescrito, una traducción de la solicitud internacional (artículo 39(1)(a)), así como también, cuando fuera aplicable, presentado una traducción de cualquier anexo del informe de examen preliminar internacional (artículo 36(3)(b) y reglamentación 74.1).

Algunas Oficinas tienen límites de tiempo fijados que expiran luego del plazo anteriormente mencionado. Para información detallada sobre el límite de tiempo aplicable y las acciones a realizar para entrar en la fase nacional ante una Oficina en particular, ver el Volumen II de la Guía para el Solicitante PCT.

El ingreso en la fase regional europea se pospone hasta 31 meses desde la fecha de prioridad para todos los Estados Designados a los fines de obtener una Patente europea.

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Oficina Internacional de WIPO.

34, chemin des Colombettes, 1211 Geneva 20, Suiza.

Fax N° (41-22) 740.14.35

Funcionario autorizado: Farid ABBOU

Teléfono N° (41-22) 338.83.38

Formulario PCT/IB/332 (septiembre de 1997)

5259185

PATENT COOPERATION TREATY

A09 6/10. 3c

RECEIVED ON 18.OCT.2002 PCT Patents, Fresnes

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Hirsch, Denise
WARNER-LAMBERT COMPANY
c/o PARKE-DAVIS
Pfizer Global Research
& Development, Fresnes Laboratories
3-9 rue de la Loge, B.P. 100
F-94265 Fresnes
FRANCE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	15.10.2002
Applicant's or agent's file reference: 018155-A305	REPLY DUE: within 1 month(s) from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP01/11330	01/10/2001	02/10/2000

International Patent Classification (IPC) or both national classification and IPC

C07D285/135

Applicant

WARNER-LAMBERT COMPANY

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 02/02/2003.

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized officer / Examiner
Allard, M

Formalities officer (incl. extension of time limits)
Smith, K
Telephone No. +31 70 340 3479

910
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WRITTEN OPINION International application No. PCT/EP01/11330

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

   Description, pages:

   1-200 as originally filed

   Claims, No.:

   1-31 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

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00/33

WRITTEN OPINION International application No. PCT/EP01/11330

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 20-22,

because:

   ☒ the said international application, or the said claims Nos. 20-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-11, 13, 31
Inventive step (IS)	Claims	
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

Reference is made to the following documents:

D1: DD 251 979 A (PÄDAGOGISCHE HOCHSCHULE 'DR. THEODOR NEUBAUER', ERFURT/MÜHLHAUSEN) 2 December 1987 (1987-12-02)

D2: HUISGEN R ET AL: '1.3-Dipolare Cycloadditionen. VI. Anlagerung der Nitrilimine an azomethine und Isocyanate' CHEMISCHE BERICHTE, vol. 97, no. 4, 3 April 1964 (1964-04-03), pages 1085-1095, XP002185163

D3: L'ABBÉ G ET AL: 'Synthesis and decomposition of functionalized diaziridinimines' JOURNAL OF ORGANIC CHEMISTRY, vol. 46, no. 22, 23 October 1981 (1981-10-23), pages 4478-4481, XP002185164

D4: CHEMICAL ABSTRACTS, vol. 73, no. 11, 14 September 1970 (1970-09-14) Columbus, Ohio, US; abstract no. 56035q, GEHLEN H ET AL: '2-Amino-1,3,4-oxadiazoles. XXXV. Synthesis and reaction of 1,3,4-oxadiazolo[3,2-a]pyrimidinones' page 322; XP002185165 & ARCH. PHARM. (WEINHEIM), vol. 303, no. 6, 1970, pages 501-510,

D5: AWASTHI A K AND AL: 'A new route to 2,3,5-trisubstituted 2,3-dihydro-1,3,4-oxadiazoles via stabilized sulfuranes' SYNTHESIS, no. 7, July 1984 (1984-07), pages 590-591, XP002185166

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Article 33(2) PCT)

Claims 1-11, 13 and 31 lack novelty in the light of the disclosure of D1, D2 (see in particular page 1087, compound XXVI), D3 (see in particular page 4479, compound 15b), D4, and D5.

Inventive step (Article 33(3) PCT)

Claims 1-11, 13 and 31, which lack novelty, cannot involve an inventive step.

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TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT. NOTIFICACION DE REMISIÓN DEL INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL (PCT, Norma 71.1)

De la: AUTORIDAD DE EXAMEN PRELIMINAR INTERNACIONAL

Para:

Hirsch, Dense

WARNER-LAMBERT COMPANY

c/o PARKE-DAVIS

Pfizer Global Research & Development, Fresnes Laboratories

3-9 rue de la Loge, B.P. 100

F-94265 Fresnes

FRANCIA

[aparece sello que reza:] Recibido el 13 de enero de 2003, Patentes. Fresnes

Fecha de envío *(día/mes/año)*: 10.01.2003

Referencia de archivo del solicitante o agente: 018155-A305

NOTIFICACIÓN IMPORTANTE

Solicitud internacional número: PCT/EP01/11330

Fecha de presentación internacional *(día/mes/año)*: 01/10/2001

Fecha de prioridad *(día/mes/año)*: 02/10/2000

Solicitante: WARNER-LAMBERT COMPANY

00439 416

Fecha de presentación internacional *(día/mes/año)*: 01/10/2001

Fecha de prioridad *(día/mes/año)*: 02/10/2000

Clasificación Internacional de Patentes (IPC) o clasificación nacional e ICP

C07D285/135

Solicitante: WARNER-LAMBERT COMPANY

1. Esta opinión escrita es la **primera** (primera) preparada por la Autoridad de Examen Preliminar Internacional.

2. Esta opinión contiene indicaciones relacionadas con los siguientes puntos:

   I. [x] Fundamento de la opinión

   II. [ ] Prioridad

   III. [x] No establecimiento de opinión sobre la novedad, paso inventivo y aplicación industrial

   IV. [ ] Falta de unidad de invención

   V. [x] Declaración fundamentada conforme a la norma 66.2(a)(ii) sobre la novedad, paso inventivo o aplicación industrial, citas y explicaciones que fundamentan dicha declaración.

   VI. [ ] Ciertos documentos citados.

   VII. [ ] Ciertos defectos en la solicitud internacional

VIII. [ ] Ciertas observaciones sobre la solicitud internacional

3. Por la presente se invita al solicitante a **responder** a esta opinión.

¿Cuándo?

Ver el plazo límite indicado arriba. El solicitante puede, antes que se venza el plazo, solicitar ante esta Autoridad que se le conceda una extensión de plazo, véase Norma 66.2(d).

¿Cómo?

Mediante la presentación de una respuesta escrita, acompañada, si fuera adecuado, por enmiendas, de acuerdo con la Norma 66.3. En cuanto al formato y al idioma de las enmiendas, véase Normas 66.8 y 66.9.

Además:

Para una oportunidad adicional para presentar enmiendas, véase Norma 66.4.

Con respecto al deber del examinador de considerar las enmiendas y/o argumentos, véase Norma 66.4 bis.

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Para una comunicación informal con el examinador, véase Norma 66.6.

Si no se presenta una respuesta, el informe de examen preliminar internacional será establecido sobre la base de esta opinión.

4. La fecha final por la cual se debe establecer el examen preliminar internacional de acuerdo con la Norma 69.2bis es: 02/02/2003

Nombre y domicilio de la autoridad de examen preliminar internacional

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Funcionario/examinador Autorizado: Allard, M

[aparece un sello en un tercer idioma]

Funcionario para formalidades (incl. Extensiones de plazo)

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OPINIÓN ESCRITA

Solicitud Internacional No. PCT/EP01/11330

1. **Fundamento de la opinión**

1. Con respecto a los **elementos** de la solicitud internacional (Las páginas reemplazantes que se han presentado ante la Oficina Receptora en respuesta a una invitación conforme al Artículo 14, se denominan en este informe "originalmente presentadas):

Memoria descriptiva, páginas:

1-200 originalmente presentadas

Reivindicaciones, No.:

1-31 originalmente presentadas

2. Con respecto al **idioma**, los elementos indicados arriba se pusieron a disposición de esta Autoridad o se presentaron ante la misma en el idioma en que se presentó la solicitud internacional, a menos que a continuación de este punto se indique lo contrario.

Estos elementos se pusieron a disposición de esta Autoridad o se presentaron ante la misma en el idioma que se indica a continuación, éste es:

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[ ] el idioma de una traducción presentada con el fin de realizar la búsqueda internacional (conforme a la Norma 23.1(b)).

[ ] el idioma de la publicación de la solicitud internacional (conforme a la Norma 48.3(b)).

[ ] el idioma de una traducción presentada a fin del examen preliminar internacional (conforme a la Norma 55.2 y/o 55.3)

3. Con respecto a cualquier **secuencia de nucleótidos y/o aminoácidos** revelada en la solicitud internacional, la opinión escrita se realizó sobre la base del listado de secuencias:

[ ] contenido en la solicitud internacional en forma escrita

[ ] presentado junto con la solicitud internacional en formato de computadora

[ ] presentado con posterioridad ante esta Autoridad en forma escrita

[ ] presentado con posterioridad ante esta Autoridad en formato de computadora

[ ] Se ha presentado la declaración que establece que el listado de secuencias escrito presentado con posterioridad no excede la revelación de la solicitud internacional.

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[ ] Se ha presentado la declaración que establece que la información registrada en forma legible por computadora es idéntica al listado de secuencias escrito.

4. Las enmiendas han dado lugar a la cancelación de:

[ ] la memoria descriptiva, páginas:

[ ] las reivindicaciones, Nos.:

[ ] las figuras, láminas:

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OPINIÓN ESCRITA

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5. [] Este informe se ha establecido como si (algunas de) las enmiendas no se hubieran introducido, ya que se ha considerado que éstas exceden la invención presentada (Norma 70.2(c)). (*Toda página reemplazante que contenga tales enmiendas debe ser citada en el punto 1 y debe anexarse a este informe.*)

6. Observaciones adicionales, si fuera necesario:

III. No establecimiento de opinión con respecto a la novedad, al paso inventivo y a la aplicación industrial

1. Las cuestiones sobre si la invención reivindicada parece ser novedosa, involucrar un paso inventivo (no ser obvia), o ser aplicable industrialmente no han sido y no serán examinadas con respecto a:

[ ] la solicitud internacional completa,

[x] las reivindicaciones Nos. 20-22.

00445 93

porque:

[x] la solicitud internacional, o las reivindicaciones Nos. 20-22 se relacionan con el siguiente objeto que no requiere un examen preliminar internacional (especificar):

ver la página aparte

[ ] la memoria descriptiva, las reivindicaciones o los dibujos (indicar los elementos particulares abajo) o las reivindicaciones Nos. son tan poco claras que no se puede formar ninguna opinión significativa (especificar):

[ ] las reivindicaciones, o las reivindicaciones Nos. están tan inadecuadamente sustentadas por la memoria descriptiva que no se puede formar ninguna opinión significativa.

[ ] no se ha establecido ningún informe de búsqueda internacional para las reivindicaciones Nos.

2. No se puede emitir una opinión escrita debido a que el listado de secuencias de nucleótidos y/o aminoácidos no cumple con la norma establecida en el Anexo C de las instrucciones administrativas:

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[ ] la forma escrita no ha sido presentada o no cumple con la norma

[ ] la forma legible por computadora no ha sido presentada o no cumple con la norma.

V. Declaración fundamentada conforme a la Norma 66.2(a)(ii) sobre la novedad, paso inventivo o aplicación industrial, citas y explicaciones que fundamentan dicha declaración.

1. Declaración

Novedad (N)	Reivindicaciones	1-11, 13, 31
Paso Inventivo (IS)	Reivindicaciones	
Aplicación industrial (IA)	Reivindicaciones	

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Solicitu Internacional No. PCT/EP01/11330

2. Citas y Explicaciones:

ver la página aparte

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00428

OPINIÓN ESCRITA

PAGINA APARTE

Solicitud Internacional No. PCT/EP01/11330

Se hace referencia a los siguientes documentos:

D1: DD 251 979 A (PÄDAGOGISCHE HOCHSCHULE 'DR. THEODOR NEUBAUER', ERFURT/MÜHLHAUSEN) 2 de diciembre de 1987 (1987-12-02)

D2: HUISGEN R ET AL: '1.3-Dipolare Cycloadditionen. VI. Anlg der Nitrilimine an azomethine und Isocyanate' CHEMISCHE BERICHTE, vol. 97, no. 4, 3 de Abril de 1964 (1964-04-03), páginas 1085-1095, HP002185163

D3: L'ABBÉ G ET AL.: 'Synthesis and decomposition of functionalized diaziridinimines' JOURNAL OF ORGANIC CHEMISTRY, vol. 46, no. 22, 23 de octubre de 1981 (1981-10-23), páginas 4478-4481, XP002185164

D4: CHEMICAL ABSTRACTS, vol. 73, no. 11, 14 de septiembre de 1970 (1970-09-14), Columbus, Ohio, US; resumen no. 56035q, GEHLEN H ET AL: '2-Amino-1,3,4-oxadiazoles. XXXV. Síntesis ad reaction of 1,3,4-oxadiazolo[3,2-a]pyrimidinones' página 322; XP002185165 & ARCH. PHARM. (WEINHEIM), vol. 303, no. 6, 1970, páginas 501-510,

004/9 427 54

D5: AWASTHI A K AND AL: 'A new route to 2,3,5-trisubstituted 2,3-dihydro-1,3,4-oxadiazoles via stabilized sulfuranes' SÍNTESIS, no. 7, julio de 1984 (1984-07), páginas 590-591, XP002185166

Re al punto III

No establecimiento de opinión con respecto a la novedad, al paso inventivo y a la aplicación industrial

Las reivindicaciones 20-22 se refieren a un objeto que esta Autoridad considera cubierto por las disposiciones de la Norma 67.1(iv) del PCT. Por lo tanto, no se formulará opinión con respecto a la aplicación industrial del objeto de estas reivindicaciones (Cláusula 34(4)(a)(I) del PCT).

Re al punto V

Declaración fundamentada conforme a la Norma 66.2(a)(ii) sobre la novedad, paso inventivo o aplicación industrial, citas y explicaciones que fundamentan dicha declaración

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OPINIÓN ESCRITA

PAGINA APARTE

Solicitud Internacional No. PCT/EP01/11330

Novedad (Cláusula 33(2) del PCT)

Las reivindicaciones 1-11, 13 y 31 carecen de novedad en vista de la revelación de D1, D2 (véase en particular la página 1087, compuesto XXVI), D3 (véase en particular la página 4479, compuesto 15b), D5 [sobre el número 5 aparece el número 4 y un signo de interrogación en letra manuscrita] y D5.

Paso inventivo (Cláusula 33(3) del PCT)

Las reivindicaciones 1-11, 13 y 31, las cuales carecen de novedad, no pueden involucrar un paso inventivo.

This page is not part of

the pamphlet!

WO 02-28847

1/2

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(75) Inventors/Applicants *(for US only)*: VERGNE, Fabrice [FR/FR]; 1, allée du champ de la mare, F-91190 Gif sur Yvette (FR). DUCROT, Pierre [FR/FR]; 6 résidence d'Amblainvilliers, F-91370 Verrieres le Buisson (FR). ANDRIANJARA, Charles [FR/FR]; 3 rue Auguste Dalx, F-94260 Fresnes (FR). BERNARDELLI, Patrick [FR/FR]; 146 rue Boucicaut, F-92260 Fontenay aux Roses (FR). LORTHIOIS, Edwige [FR/FR]; 6 rue de la Briquetterie, F-75014 Paris (FR).

(74) Agent: HIRSCH, Denise; Warner-Lambert Company, c/o Parke-Davis, Pfizer Global Research & Development, Fresnes Laboratories, 3-9 rue de la Loge, F-94265 Fresnes (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW THIADIAZOLES AND OXADIAZOLES AND THEIR USE AS PHOSPHODIESTERASE-7 INHIBITORS

(57) Abstract: The invention provides 1,3,4-thiadiazoles and 1,3,4-oxadiazoles having the following formula (I):in which, Y is S or O,R1 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, heteroaryl or a polycyclic group, optionally substituted,R2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl or aryl optionally substituted,R3 is X_2-R'3, in which X_2 is a binding group and R'3 is cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, heteroaryl, or a polycyclic group; optionally substituted,or their pharmaceutically acceptable derivatives,the process for their preparation and their use for the manufacture of a medicament for the treatment of disorders for which a treatment by a PDE7 inhibitor is relevant.

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NEW THIADIAZOLES AND OXADIAZOLES AND THEIR USE AS PHOSPHODIESTERASE-7 INHIBITORS

Field of the invention.

The invention relates to novel thiadiazoles and oxadiazoles, processes for their preparation, and their use as phosphodiesterase 7 (PDE7) inhibitors.

Background of the invention.

Phosphodiesterases (PDE) play an important role in various biological processes by hydrolysing the key second messengers adenosine and guanosine 3',5'-cyclic monophosphates (cAMP and cGMP respectively) into their corresponding 5'-monophosphate nucleotides. Therefore, inhibition of PDE activity produces an increase of cAMP and cGMP intracellular levels that activate specific protein phosphorylation pathways involved in a variety of functional responses.

At least eleven isoenzymes of mammalian cyclic nucleotide phosphodiesterases, numbered PDE 1 through PDE 11, have been identified on the basis of primary structure, substrate specificity or sensitivity to cofactors or inhibitory drugs.

Among these phosphodiesterases, PDE7 is a cAMP-specific PDE. The biochemical and pharmacological characterisation showed a high-affinity cAMP-specific PDE (Km=0.2 μM), that was not affected by cGMP potent selective PDE isoenzyme inhibitors.

PDE7 activity or protein has been detected in T-cell lines, B-cell lines, airway epithelial (AE) cell lines and several foetal tissues.

Increasing cAMP levels by selective PDE7 inhibition appears to be a potentially promising approach to specifically block T-cell mediated immune responses. Further studies have demonstrated that elevation of intracellular cAMP levels can modulate inflammatory and immunological processes. This selective approach could presumably be devoid

of the side effects associated with known selective inhibitors (e.g. PDE3 or PDE4 selective inhibitors) and which limit their use.

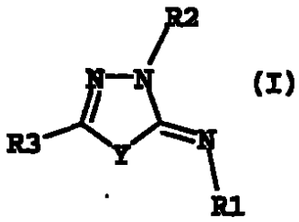
A functional role of PDE7 in T-cell activation has als been disclosed; therefore selective PDE7 inhibitors would be candidates for the treatment of T-cell-related diseases.

AE cells actively participate in inflammatory airway diseases by liberating mediators such as arachidonate metabolites and cytokines. Selective inhibition of PDE7 may be a useful anti-inflammatory approach for treating AE cells related diseases.

Thus, there is a need for selective PDE7 inhibitors, which are active at very low concentrations, i.e. micromolar inhibibitor, preferably nanomolar inhibitors.

Summary of the invention.

The invention provides pharmaceutical compositions comprising a compound having the following formula (I):



wherein:

- Y is O or S;
- R1 is:
  - C_1-C_{10} alkyl,
  - C_2-C_{10} alkenyl,
  - C_2-C_{10} alkynyl,
  - cycloalkyl,
  - cycloalkenyl,
  - heterocycle,
  - aryl,
  - or a polycyclic group;

each optionally substituted with one or several groups X_1-R_4,

identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_2-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
2) $COOR_5$, OR_5, SO_2R_5,
3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:

- X_2 is a single bond or,
  a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
  1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
  2) OR_5, $=NR_5$ or,
  3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R'3 is:
cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;
each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5;

wherein,

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-N(R_{18})(R_{19}) in which X_5 is a single bond or lower alkylene and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;
  - X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;
- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{18})(R_{19}) in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;
- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

together with a pharmaceutically acceptable carrier,
with the proviso that the compound of formula (I) is not 4-[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-butyric acid ethyl ester,
4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-butyric acid ethyl ester.

The invention also relates to novel compounds having the following formula (I) above.

These compounds are selective PDE7 inhibitors. They can be used in the treatment of various diseases, such as T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, central nervous system (CNS) diseases, allergic diseases, endocrine or exocrine pancreas diseases, gastrointestinal diseases, visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

The invention also relates to a process for preparing the above compounds.

The invention further concerns the use of a compound f formula (I) for the preparation of a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

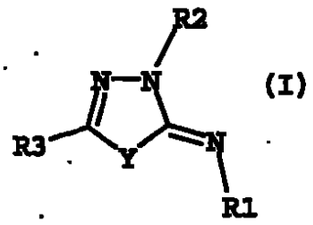
The invention also provides a method for the treatment of a disorder for which therapy by a PDE7 inhibitor is relevant, comprising administering to a mammal in need thereof an effective amount of compound of formula (I).

The invention also concerns a pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for the treatment of a disorder for which therapy by a PDE7 inhibitor is relevant, comprising a compound f formula (I) together with a pharmaceutically acceptable carrier.

Detailed description of the invention.

The present invention provides pharmaceutical compositions comprising compounds having formula I,



in which R1, R2, R3 and Y are as defined above with the exclusion of the compounds recited above.

In the following and in the foregoing text:

- aryl is understood to refer to an unsaturated carbocycle, exclusively comprising carbon atoms in the cyclic structure, the number of which is between 5 and 10, including phenyl, naphthyl or tetrahydronaphthyl;

- heterocycle is understood to refer to a non-saturated or saturated monocycle containing between 1 and 7 carbon atoms in the cyclic structure and at least one heteroatom in the cyclic structure, such as nitrogen, oxygen, or sulfur, preferably from 1 to 4 heteroatoms, identical or different, selected from nitrogen, sulfur and oxygen atoms. Suitable heterocycles include morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, pyrimidinyl, 2- and 3-furanyl, 2- and 3-thienyl, 2-pyridyl, 2- and 3-pyranyl, hydroxypyridyl, pyrazolyl, isoxazolyl, tetrazole, imidazole, triazole and the like;

- polycyclic groups include at least two cycles, identical or different, selected from aryl, heterocycle, cycloalkyl, cycloalkenyl groups fused together to form said polycyclic group such as 2- and 3-benzothienyl, 2- and 3-benzofuranyl, 2-indolyl, 2-. and 3-quinolinyl, acridinyl, quinazolinyl, indolyl benzo[1,3]dioxolyl and 9-thioxantanyl;
Preferred polycyclic groups include 2 or 3 cycles as defined above.
More preferred polycyclic groups include 2 cycles (bicyclic substituents) as defined above.

- bicyclic groups refer to two cycles, which are the same or different and which are chosen from aryl, heterocycle, cycloalkyl or cycloalkenyl, fused together to form said bicyclic groups;

- halogen is understood to refer to fluorine, chlorine, bromine or iodine;

- lower alkyl is understood to mean that the alkyl is linear or branched and contains 1 to 6 carbon atoms; Examples of lower alkyl groups include methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, isobutyl, n-butyl, pentyl, hexyl and the like.

- alkenyl is understood to refer to a linear or branched unsaturated carbon atom chain, comprising one or several double bonds, preferably one or two double bonds. Preferred alkenyls comprise from 3 to 6 carbon atoms and one double bonds.

- alkynyl is understood to refer to a linear or branched unsaturated carbon atom chain, comprising one or several triple bonds, preferably one or two triple bonds. Preferred alkynyls comprise from 3 to 6 carbon atoms and one triple bonds.

- lower haloalkyl are understood to refer to a lower alkyl substituted with one or several halogens; Preferred lower haloalkyl groups include perhaloalkyl groups such as CF_3.

- cycloalkyl is understood to refer to saturated monocarbocyle containing from 3 to 10 carbon atoms; preferred cycloalkyl groups comprise cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

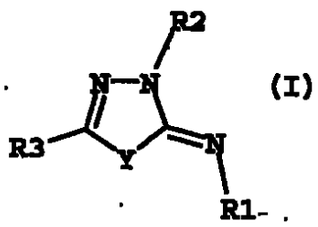
- cycloalkenyl is understood to refer to unsaturated monocarbocyle containing from 3 to 10 carbon atoms. Preferred cyloalkenyl groups contain 1 or 2 double bonds. Examples f suitable cycloalkenyl are 3-cyclohexene, 3-cycloheptene or the like.

- carboxylic acid bioisostere has the classical meaning; common carboxylic acid bi isostere are tetrazol, hydroxamic acid, isoxazole, hydroxythiadiaz le, sulfonamide, sulfonylcarboxamide, phosphonates, phosphonamides,

phosphinates, sulfonates, acyl sulfonamide, mercaptoazole, acyl cyanamides.

Preferred pharmaceutical composition are those containing a compound of formula (I) in which R1, R2, R3 and Y are as defined above, with the proviso that when R1 is C(=O)-H, then R2 does not represent $(CH_2)_3$-C(=O)OCH_2CH_3.

The present invention also relates to compounds of formula (I),



in which

- Y is O or S;
- R1 is:
  - C_4-C_{10} alkyl,
  - C_2-C_{10} alkenyl,
  - C_2-C_{10} alkynyl,
  - cycloalkyl,
  - cycloalkenyl,
  - heterocycle,
  - aryl,
  - or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5,

OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_4-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
2) $COOR_5$, OR_5, SO_2R_5,
3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
    2) OR_5, $=NR_5$ or,
    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or

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different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:

a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,

- R_{17} is:

1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

4) heterocycle optionally substituted with one or several groups R_5;

wherein, R_5, R_6, R_9 and R_{10} are as defined above,

with the proviso that,

- when R1 is phenyl, it bears at least one substituent other than H,

- when X_2 is a single bond and both R1 and R'_3 are phenyl, each of R1 and R'_3 bear at least one substituent other than H,

- when X_2 is a single bond and R'_3 is phenyl, R'_3 is not substituted by an ester or a carboxylic acid in the ortho position,

- the atom of R3 which is linked to the thiadiazole group is a carbon atom,

with the exclusion of the following compounds,

1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-methanone,

1-[4-Phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,

1-Phenyl-1-(4-phenyl-5-*p*-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,

Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethyl-cyclopent-1-enylmethyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,

2-(3,5-Diphenyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,

2-[3-Phenyl-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,

2-[5-(1-Phenyl-methanoyl)-3-*p*-tolyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,

2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

Preferred compounds of formula (I) are those in which R1, R2, R3 and Y are as defined above, with the proviso that, when R2 is a phenyl, unsubstituted or substituted whith 1 t 3 chorine or with a methyl, then R3 does not represent C(=O)-phenyl, C(=O)-thienyl, phenyl or CH_2-(2,3,3-trimethyl-cyclopent-1-enyl).

Other preferred compounds of formula (I) are those in which

- R1 is:
  - C_4-C_6 alkyl,
  - cycl alkyl,
  - cycloalkenyl,

heterocycle,
aryl,
or a bicyclic group;
each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:
  1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$.

Other preferred compounds of formula (I) are those in which R2 is lower alkyl.

Further preferred compounds of formula (I) are those in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene and,
- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;
each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$,

$C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5.

Particularly preferred compounds of formula (I) are those in which R1 is:

cycloalkyl, preferably cyclohexane,
cycloalkenyl,
aryl, preferably phenyl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$.

Other particularly preferred compounds of formula (I) are those in which R2 is CH_3.

Further particularly preferred compounds of formula (I) are those in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or $-CH_2-$, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

More preferred compounds of formula (I) are those in which

- R1 is:
  C_4-C_6 alkyl
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl,
  or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:
  1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$,

R2 is lower alkyl, and,

R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene and,

- R'3 is:
cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;
each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:
- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
4) heterocycle optionally substituted with one or several groups R_5.

Other more preferred compounds of formula (I) are those in which,
R1 is:
cycloalkyl, preferably cyclohexane,
cycloalkenyl,
aryl, preferably phenyl,
or a bicyclic group;
each optionally substituted with one or several groups X_1-R_4, identical or different, in which:
- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
1) H, halogen, CF_3, =O,
2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$,

R2 is CH_3, and,

R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or $-CH_2-$, and,
- R_{17} is:

1) H, CN, CF_3, halogen, NO_2

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5.

Other more preferred compounds of formula (I) are those in which,

Y is O,

R1 is:

cycloalkyl, preferably cyclohexane,
cycloalkenyl,
aryl, preferably phenyl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,

- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$,

R2 is CH_3, and,

R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or $-CH_2-$, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one r several groups R_5.

More specifically, a group of compounds of formula (I) which has been found to be of particular interest are those in which,

R1 is:

cyclohexane,
phenyl
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3,
  2) COOH, OH,
  3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same or different and are selected from H or lower alkyl,

R2 is CH_3, and,

R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond, and,
- R_{17} is:
  1) CN, OH, CF_3, =O, C_1-C_6 alkoxy, halogen,
  2) $COOR_5$, SO_2R_5,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 or R_6,
  4) heterocycle optionally substituted with one or several groups R_5.

Most preferred compounds of formula (I) are those in which Y is S.

Preferably, in each of the above definition of R1:

- R_5 is selected from
  - H, or,
  - lower alkyl, optionally substituted with OH, preferably CH_3.
- R_6 is selected from

- H, or,
- lower alkyl,preferably CH_3.

- R_9 and R_{10} are selected from
  - H, or,
  - lower alkyl, preferably CH_3.

Preferably, in each of the above definition of R2:

- R_5 and R_6 are selected from
  - H, or,
  - lower alkyl, preferably CH_3.
- R_9 and R_{10} are selected from:
  - H, or,
  - lower alkyl, preferably CH_3.

Preferred compounds are:

I1	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I1.1	(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
I1.2	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol
I1.7	2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol
I1.9	{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol
I1,10	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
I2.1	5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiaz 1-2-ylideneamino]-2-fluoro-benzoic acid
I2.2	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid
I3	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-propyl-amine
I3.1	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1- l

I3.3	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiaz l-2-ylidene]-cyclobutyl-amine
I3.4	3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one
I3.7	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine
I3.8	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiaz l-2-ylidene]-cycloheptyl-amine
I3.10	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol
I3.11	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol
I3.13	tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I3.14	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylidene]-isopropyl-amine
I3.15	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I3.16	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylidene]-(1-ethyl-propyl)-amine
I3.17	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I3.18	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine
I3.19	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylidene]-(4-fluoro-phenyl)-amine
I3.20	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine
I3.25	(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
I3.26	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylidene]-(4-trifluoromethyl-phenyl)-amine
I4	3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylideneamino]-benzoic acid
I5	3-[5-(4-Chl ro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylideneamino]-phenol

I6	5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid
I6.1	(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.3	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I6.5	(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol
I6.7	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine
I6.8	(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.9	{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid
I6.11	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide
I7	Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I8	(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
I8.1	5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol
I8.2	3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid
I8.3	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benz ic acid
I8.4	(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine
I9	(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
I10	Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I10.1	[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylidene]-cyclohexyl-amine

I11 Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine

I12 Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

I13 [5-(3-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I14 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

I15 Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I15.1 [3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine

I15.2 Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine-

I16 2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

I17 Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

I17.1 Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I17.2 Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I18 [5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I18.1 Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

I18.2 Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I18.3 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid

I18.4 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid

I18.5 [5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I18.6 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

I19 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

I19.1 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide

I19.2 {5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine

I19.3 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide

I19.4 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

I19.5 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide

I19.6 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

I19.7 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

I19.8 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide.

I19.9 C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide

I19.10 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide

I19.11 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide

I19.12	2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide
I19.14	2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide
I20	[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester
I21	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester
I21.1	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid
I21.2	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
I21.3	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide
I21.4	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide
I22	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol
I23	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol
I23.1	6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol
I23.2	5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol
I24	2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol
I25	Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
I26	5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol
I27	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol
I28	Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

I29 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine

I30 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

I31 [5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid

I31.1 2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

I32 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

I33 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

I34 Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I35 [5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I35.1 Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I35.2 Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

I36 3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol

I37 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I37.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid

I37.2 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide

I37.3 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I37.4 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz l-2-yl)-*N*-(2H-tetrazol-5-yl)-benzamide hydrochloride salt

I37.5	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide
I37.6	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide
I37.7	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide
I37.8	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide
I37.8-1	Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine
I37.9	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide
I37.10	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide
I37.11	2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide
I37.12	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide
I37.13	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide
I37.13-1	4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide
I37.14	[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone
I37.15	2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
I37.15-a	(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid; compound with 2,2,2-trifluoro-acetic acid,

I37.16 (S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,

I37.16-a (S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid

I37.17 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone

I37.18 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone

I37.19 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide

I37.20 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,

I37.21 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone

I37.22 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide

I37.23 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide

I37.24 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide

I37.25 N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I37.26 N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I37.27 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz l-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide

I37.28	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide
I37.28-1	[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
I37.29	4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide
I38	Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
I39	3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide
I40	(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine
I41	Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I42	4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
I43	4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
I44	4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I45	4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I46	5-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiaz I-2-ylideneamino]-2-fluoro-benzoic acid
I47-a	4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I47-b	4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I48	4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I49	4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

I50 4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

I51 4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

I52-a 4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

I52-b 4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

I53 (1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

I54 4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid

I55 4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide

I56 4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid

I57 4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

I58 4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

I59 N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

I60 N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

I61 N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

I62	1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester
I63	4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
I64	4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
I65	4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I66	4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I67	5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid
I68	4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I69	4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I70	4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I71	4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I72	4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I73	4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I74	4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I74.1	4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I75	4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I76	4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide
I77	4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl]-benzamide

I78	(1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol
I79	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid
I80	3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylideneamino]-benzoic acid
I80.1	3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I81	2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I82	3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
I83	[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine
I84	[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine
I85	3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I86	N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide
I87	N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide
I88	N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide
I89	*N*-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide
I90	3-[5-(4-Chloro-phenyl)-3-methyl-3H/-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile
I90.1	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetraz l-5-yl)-phenyl]-amine

I90.2 3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine

I90.3 3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol

I91 [5-(4-Bromo-3-methyl-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I91.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile

I91.2 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide

I92 [5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

I92.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide

I92.2 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide

I93 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester

I93.1 2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I93.2 2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I93.3 2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I93.4 7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one

I93.5 7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine

I93.6 7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione

I94 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide

I95 5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide

I96 3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester

I96.1 3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I97.1 3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I98 3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I99 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

I99.1 Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine

I100 Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

I100.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine

I100.2 [5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I100.3 N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide

I100.4 [5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

I100.5 [5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)- phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I100.6 (E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine

I100.7 [5-(N-cyano-N'-methyl-4-carboximidamide-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I100.8 [5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

I100.9 Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide

I100.10 [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-phenyl]-urea

I100.11 1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea

I101 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

I102 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I102,1 2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I103 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I104 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester

I104.1 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide

The compounds utilised in the invention include pharmaceutically acceptable derivatives of compounds of formula (I) such as solvates, hydrates, pharmaceutically acceptable salts and polymorphs (different crystalline lattice descriptors).

Pharmaceutically acceptable salts of a compound of formula (I) include salts having a basic part and salts having an acidic part.

The expression pharmaceutically acceptable salt of a compound of formula (I) having a basic part should be understood to refer to the addition salts of the compounds f formula (I) which may be formed from non-toxic inorganic r organic acids such as, for example, hydrobromic, hydrochloric, sulfuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic, hydroxymaleic, benzoic, fumaric, toluenesulfonic and isethionic acid salts, and the like. The various quaternary ammonium salts of the derivatives (I) are als included in this category f compounds f the invention. In addition, the expression pharmaceutically acceptable salt f a compound of f rmula (I) having an acidic part is

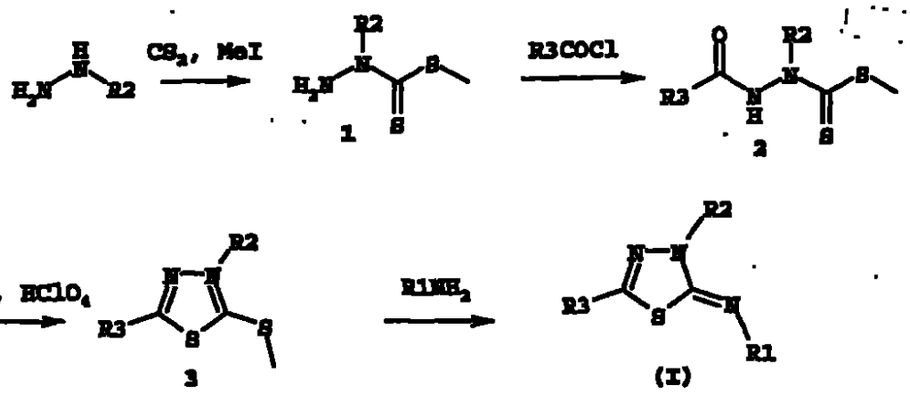
understood to refer to the usual salts of the compounds f formula (I) which may be formed from non-toxic inorganic r organic bases such as, for example, the hydroxides of alkali metals and alkaline-earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or alternatively quaternary ammonium hydroxides such as tetramethylammonium hydroxide. (See also "Pharmaceutical salts" by Berge S.M. *et al.* (1997) J. Pharm. Sci. 66: 1-19, which is incorporated herein by reference.).

Use of a prodrug of a compound of the invention such as would occur to one skilled in the art (see Bundgaard, et al., Acta Pharm. Suec., 1987; 24: 233-246), is also contemplated.

Process for the preparation.

The compounds of this invention can be synthesised according to the general procedures of synthesis A-E, utilising methodology described herein which is known to a person skilled in the art.

Protocol A:



The starting compounds are either commercially available or can be prepared according to routes known to

the skilled man. See M. Akbar Ali, S.E. Livingston, and D.J. Philipps, *Inorganica Chimica Acta*, 6, 11 (1972); P. Molina, A. Tarraga, A. Espinosa; *Synthesis*, 690 (1988); P. Molina, A. Tarraga, A. Espinosa; *Heterocycles*, vol.29, N°12 (1989).

In step 1, the substituted hydrazine is reacted with carbon disulphide and with an alkyl-iodide such as methyl-iodide to form the desired 2-substituted S-alkyldithiocarbazate (1). Various solvents, operating conditions, bases, can be used and will be easily determined by the skilled person. For example, and without any limitation, one can use for the reaction of the substituted hydrazine with carbon disulphide an alcoholic solution of potassium hydroxide with a temperature not exceeding 15°C. Methyl iodide can be added to this solution or to a diluted solution (e.g. with water).

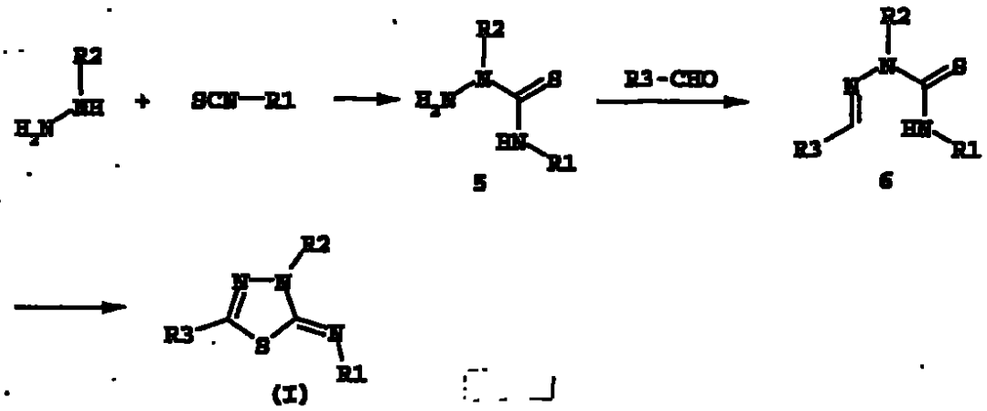
In step 2, the substituted S-methyldithiocarbazate is reacted with an appropriate group R3CO-X in which X is a leaving group such as halogen. Preferably, R3CO-X is an acyl chloride (R3COCl). The reaction can be carried out in e.g. toluene as the solvent at reflux. The corresponding acylated methyldithiocarbazate (2) is obtained.

In step 3, the acylated methyldithiocarbazate is cyclized into the desired 1,3,4-thiadiazole. The reaction can be carried out in the presence of acetic anhydride (AA) and perchlorate $HClO_4$ in ether, preferably, at a temperature comprised between -5 and 5°C, preferably 0°C, or in the presence of trimethylsilyl trifluoromethanesulfonate in dichloromethane, preferably, at a temperature comprised between 0 and 25°C. After stirring at room temperature several hours, an intermediate compound which is the 1,3,4-thiadiazolium perchlorate (3) is obtained.

In step 4, the 1,3,4-thiadiazole (or its perchlorate or sulfonate) is reacted with a suitable amine $R1NH_2$, to form the final compound. The reaction can be carried out in alcool such as ethanol as a solvent (the solvent may also be an aprotic solvant such as dioxane, dimethylformamide (DMF) or acetonitrile), in the presence of a base such as

triethylamine, and preferably, at a temperature comprised between 40 and 110°C, preferably between 40 and 80°C.

Protocol B :



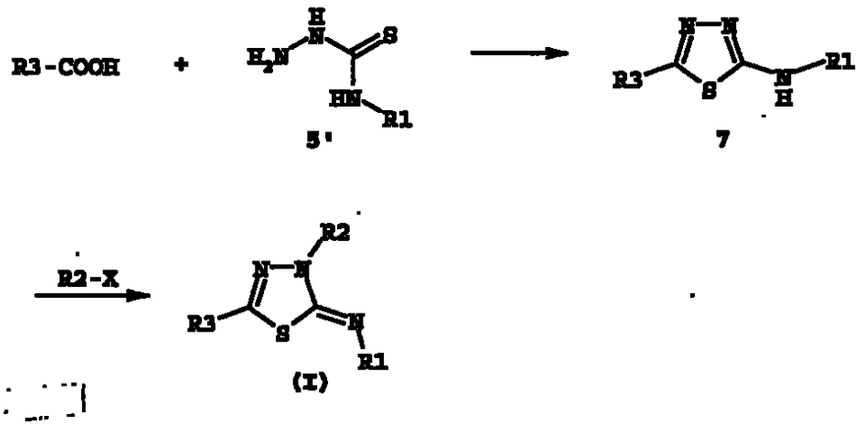
The starting compounds are either commercially available r can be prepared according to routes known to the skilled person. See R. Noto, P. Lo Meo, M. Gruttadauria, G. Werber ; *J. Heterocyclic Chem.*, 33, 863 (1996).

In step 1, the substituted isothiocyanate is reacted with the substituted hydrazine to form the desired substituted thiosemicarbazide (5). The reaction can be carried out in alcool e.g. methanol and/or water at a temperature comprised between -5°C and 15°C, preferably 0°C.

In step 2, the substituted thiosemicarbazide is reacted with an aldehyde R3CHO to form the desired thiosemicarbazone (6). The reaction can be carried out in alcool e.g. methanol, at a temperature comprised between 50 and 90°C, preferably 75°C.

In step 3, the substituted thiosemicarbazone is cyclized to yield compound (I). The reaction can be carried out in alcool, e.g. ethanol, at a temperature comprised between 20°C and 110°C, preferably 75°C, in the presence of an oxidant such as $FeCl_3$.

Protocol C :

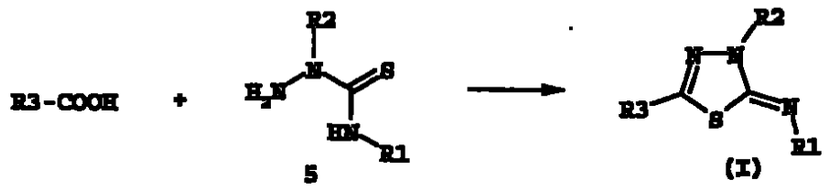


The starting compounds are either commercially available or can be prepared according to routes known to the skilled man. See FR-A-7712352, DE-A-4418066 and FR-A-8015072.

In the first step, the carboxylic acid is reacted with the thiosemicarbazide derivative (5') to yield the desired 1,3,4-thiadiazole (7). The reaction can be carried out in an aprotic solvant such as dioxane, at reflux, in the presence of a deshydrating agent, eg $POCl_3$.

In the second step, the desired 1,3,4-thiadiazole is reacted with R2X, where X is a leaving group such as trifluoromethane sulfonate, iodide or bromide. The reaction can be carried out in an aprotic solvent such as dioxane or DMF (if R2-X is alkyl-iodide or bromide), preferably at room temperature (RT) or under heating to yield compound (I).

Protocol D : 1 step



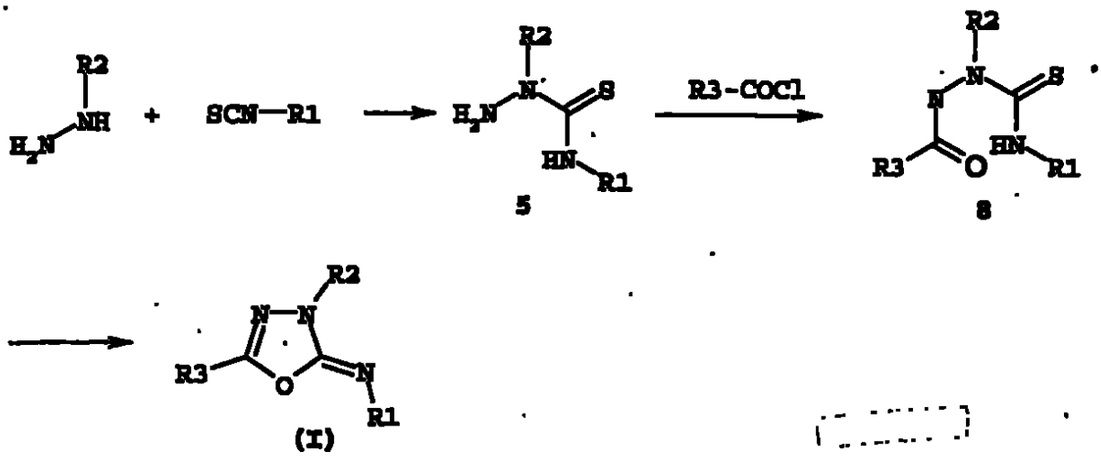
The starting compounds are either commercially available or can be prepared according to routes known to the skilled man.

In the first step, the carboxylic acid is reacted with the substituted thi semicarbazide derivative (5) t yield

the desired final 1,3,4-thiadiazole (I). The reaction can be carried out in an aprotic solvent such as dioxane, at reflux and at a temperature comprised between 75 and 120°C, in the presence of a deshydrating agent, e.g $POCl_3$.

The solvent, reaction time, temperature, catalyst if any, can be varied in all steps described above for all routes, as the skilled man will appreciate.

Protocol E : 3 step



See J.M. Kane, M.A. Staeger, Synthetic communication, 22 (1), 1-11 (1992).

The starting compounds are either commercially available or can be prepared according to methods known to the skilled person. See R. Noto, P. Lo Meo, M. Gruttadauria, G. Werber ; J. Heterocyclic Chem., 33, 863 (1996).

In step 1, the substituted isothiocyanate is reacted with the substituted hydrazine to form the desired substituted thiosemicarbazide (5). The reaction can be carried out in alcool e.g. methanol and/or water at a temperature comprised between -5 and 15°C preferably 0°C.

In step 2, the substituted thiosemicarbazide is reacted with the acid chloride to form the desired thiosemicarbazide (8). The reaction can be carried out in a basic medium such as pyridine at room temperature, r in an aprotic solvent in the presence f a base such as pyridine or triethylamine.

In step 3, the substituted thi semicarbazide is

cyclized to yield compound (I). The reaction can be carried out in alcool, e.g. methanol, at a temperature of e.g. 75°C, in the presence of Mercuric oxide (HgO).

Pharmaceutical compositions.

The products of the invention are administered in the form of compositions, which are appropriate depending on the nature, and severity of the condition to be treated. The daily dose in humans is usually between 2 mg and 1 g of the active ingredient, which may be taken in one or more individual doses. The compositions are prepared in forms which are compatible with the intended route f administration, such as, for example, tablets, coated tablets, capsules, mouthwashes, aerosols, powders f r inhalation, suppositories, enemas, foams (such as rectal foams) gels or suspensions. These compositions are prepared by methods which are familiar to those skilled in the art and comprise from 0.5 to 60% by weight of active ingredient (compound of the invention) and 40 to 99.5% by weight of a pharmaceutical vehicle or carrier which is appropriate and compatible with the active principle and the physical form f the intended composition.

Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may als act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders, tablets, cachets or encapsulated forms for capsules preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl

cellulose, a low-melting wax, cocoa butter, and the like.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration. The drug may be delivered as a spray (either in a pressurised container fitted with an appropriate valve or in a non-pressurised container fitted with a metering valve).

Liquid form preparations include solutions, suspensions, and emulsions.

Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavouring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and coc a butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify. Enemas are obtained according to known procedures to prepare solutions adapted for rectal administration. Foams are prepared according to known methods (these foams can notably be similar to those used to administer a drug such as 5-ASA for treating rectocolite).

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided int unit doses containing appropriate quantities of drug. The unit dosage f rm can be a packaged preparation, the package containing discrete quantities f the preparation, for

example, packaged tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Methods of treatment.

The compounds of the invention are selective PDE7 inhibitors. They can be used in the treatment of various diseases, as they can modulate inflammatory and immunological processes due to an increase of intracellular cAMP levels.

The diseases that can be successfully treated include namely T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, gastrointestinal diseases, visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

The compounds of the invention have low IC50 values, typically at most 5 μM, preferably below 1 μM, and even below 100 nM.

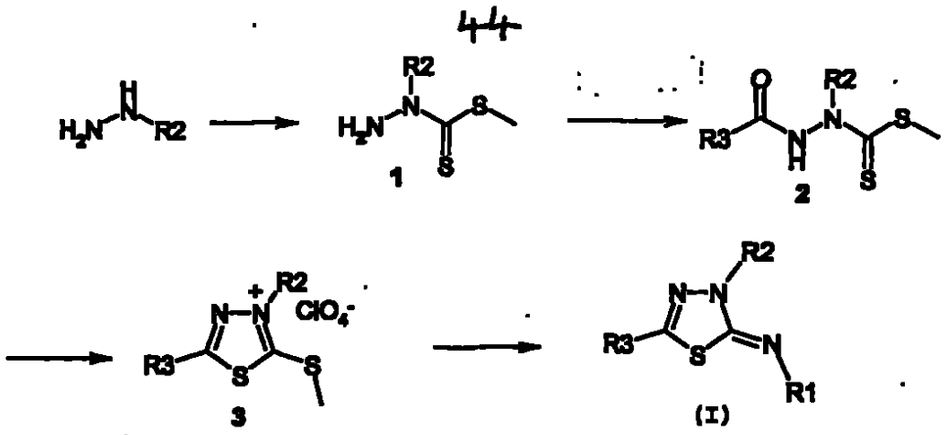
The invention finally relates to a method for the treatment of the above-mentioned diseases comprising administering to a mammal, particularly a human, in need thereof an effective amount of compound of the invention.

The following examples illustrate the invention without limiting it.

Examples

Compounds of the invention have been named with the software "AutoNom Version 4.0"

Protoc 1 A :



Intermediate 1 : PROTOCOL A

Intermediate 1a: R2= methyl
***N*-Methyl-hydrazinecarbodithioic acid methyl ester**

Methylhydrazine (370 mmol, 19.43 ml) was added t a solution of potassium hydroxide (370 mmol, 20.7 g) in 90% aqueous alcohol (130 mL). The mixture was cooled to 5°C, then carbon disulphide (370 mmol, 22.2 ml) was added dropwise with vigorous stirring, over 1h, while the temperature of the mixture was not allowed to rise above 7°C. The resulting yellow solution was diluted with water (300 ml) and the methyl iodide (370 mmol, 23.34 ml) was added slowly while the mixture was stirred vigorously. After the stirring had been continued for 3 h at 10-15°C, the white crystals of 2-methyl-S-methyldithiocarbazate (1a) were filtered off, washed with a mixture 1:1 of ethanol:petroleum ether to give 38 g of the desired compound.

Yield: 84%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.32 (s, 3H), 3.60 (s, 3H), 5.55 (s, 2H).

Intermediate 2: PROTOCOL A

Intermediate 2a: R2= methyl, R3= 4-chloro-phenyl
***N'*-[1-(4-Chloro-phenyl)-methanoyl]-*N*-methyl-hydrazinecarbodithioic acid methyl ester**

The appropriate acyl chloride (73.39 mmol, 9.30 ml) (R3COCl)

was added to a suspension of 2-methyl-S-methyldithiocarbazate (73.39 mmol, 10 g) in toluene (80 ml). The mixture was stirred at reflux for 4h then allowed t cool down overnight. The solids were isolated by filtration, washed with water and then with ether to give 15 g of the expected 3-acyl-2-methyl-S-methyldithiocarbazate (2a).
Yield= 74%

^{1}H-NMR (400MHz, DMSO) δppm: 2.45 (s, 3H), 3.65 (s, 3H), 7.65 (dd, 2H), 7.90 (dd, 2H), 11.68 (s, 1H).

Intermediate 2b: R2= methyl, R3= 4-(methylsulfonyl)-phenyl
N'-[1-(4-Methanesulfonyl-phenyl)-methanoyl]-N-methyl-hydrazinecarbodithioic acid methyl ester
The acid chloride was prepared from the corresponding benzoic acid.
The appropriate acyl chloride (1.68 mmol, 0.39 g) was added to a suspension of 2-methyl-S-methyldithiocarbazate (1.77 mmol, 0.24 g) in toluene (2 ml). After 5h at reflux, the mixture was cooled down overnight, triturated in ether and stirred over 2 h at RT to give 440 mg of the expected product (2b) as a white solid.
Yield= 82%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.5 (s, 3H), 3.30 (s, 3H), 3.65 (s, 3H), 8.15 (m, 4H), 11.9 (s, 1H).

Intermediate 2c: R2= methyl, R3= 4-cyano-phenyl
N'-[1-(4-Cyano-phenyl)-methanoyl]-N-methyl-hydrazinecarbodithioic acid methyl ester
The appropriate acyl chloride (22.77 mmol, 3.77 g) (R3COCl) was added to a suspension of 2-methyl-S-methyldithio carbazate (22.77 mmol, 3.10 g) in toluene (25 ml). The mixture was stirred at reflux for 3h-3h30 then allowed to cool down overnight. The solids were isolated by filtration, washed with water then with ether and dried to give 4.15 g of the expected 3-acyl-2-methyl-S-methyldithiocarbazate (2c).
Yield= 68%

^{1}H-NMR (400MHz, DMSO) δppm: 2.45 (s, 3H), 3.65 (s, 3H), 8.05 (m, 4H), 11.85 (s, 1H).

Intermediate 2d: R2= methyl, R3= 4-acetyamino-phenyl
N'-(4-Acetylamino-benzoyl)-N-methyl-hydrazinecarbodithioic acid methyl ester

The acid chloride was prepared from the corresponding benzoic acid.

To a suspension of the appropriate acyl chloride (10 mmol, 1.4 g) in toluene (30 ml), was added triethylamine (20 mmol, 2.8 ml) followed by 2-methyl-S-methyldithiocarbazate (12 mmol, 2.4 g). The mixture was maintained at 90°C for 2 hours and was concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and washed with AcOEt to give 1.28 g of the title compound.

Yield= 45%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.10 (s, 3H), 2.45 (s, 3H), 3.65 (s, 3H), 7.85 (d, 2H), 7.90 (d, 2H), 10.30 (s, 1H), 11.40 (s, 1H).

Intermediate 2e: R2= methyl, R3= 4-acetylamino-3-pyridyl
N'-(6-Acetylamino-pyridine-3-carbonyl)-N-methyl-hydrazinecarbodithioic acid methyl ester

The acid chloride was prepared from the corresponding benzoic acid.

To a suspension of the appropriate acyl chloride (63 mmol, 11 g) in toluene (150 ml) was added triethylamine (130 mmol) followed by 2-methyl-S-methyldithiocarbazate (62 mmol, 9 g). After 3h at room temperature, the mixture was concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and purified by chromatography on silica gel (95:5 (dichloromethane (DCM)/MeOH) to give 9 g of the title compound.

Yield= 50%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.15 (s, 3H), 2.45 (s, 3H), 3.65 (s, 3H), 8.25 (m, 2H), 8.80 (s, 1H), 10.90 (s, 1H).
MS (m/z) / M+1= 298.99

Intermediate 3: PROTOCOL A

Intermediate 3a: R2= methyl, R3= 4-chloro-phenyl 1,3,4-Thiadiazolium, 5-(4-chlorophenyl)-3-methyl-2-(methylthio)-perchlorate

To a suspension of the (2a) (54.4 mmol, 15 g) in ether (150 ml) at 0°C, acetic anhydride (30 ml) was added slowly and then $HClO_4$ 70% (65.33 mmol, 5.61 ml) was added dropwise at 0°C for 1 hour. The resultant mixture was stirred at RT overnight and the precipitate separated by filtration, was washed with ether and then air dried to give 19 g of the title compound (3a) as white solid.
Yield= 97%.
^{1}H-NMR (400MHz, DMSO) δ ppm: 2.92 (s, 3H), 3.99 (s, 3H), 7.52 (dd, 2H), 7.82 (dd, 2H).
MS (m/z) / M+1 = 257/259

Intermediate 3b : R2= methyl, R3= 4-(methylsulfonyl)phenyl 1,3,4 - Thiadiazolium, 5-(4-Methanesulfonyl-phenyl)-3-methyl-2-(methylthio)-perchlorate

To a suspension of the (2b) (0.69 mmol, 0.22 g) in ether (3 ml) at 0°C, acetic anhydride (0.4 ml) was added slowly and then $HClO_4$ 70% (0.90 mmol, 0.080 mL) was added dropwise at 0°C for 1 hour. The resultant mixture was then allowed t rise to RT and stirred for 3h. The precipitate was isolated by filtration then air dried to give 220 mg of the expected 3-methyl-2-methylthio[1,3,4]thiadiazolium perchlorate (3b) as a white solid.
Yield= 78%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.14 (s, 3H), 3.33 (s, 3H), 4.20 (s, 3H), 8.20 (dd, 2H), 8.25 (dd, 2H).
MS (m/z) / M+1 = 301/303

Intermediate 3c: R2= methyl, R3= 4-cyano-phenyl 1,3,4 - Thiadiazolium, 5-(4-cyanophenyl)-3-methyl-2-(methylthio)-perchlorate

To a suspension of intermediate (2c) (15.64 mmol, 4.15 g) in ether (50 ml) and acetic anhydride (13.3 ml), $HClO_4$ 70% (18.76 mmol, 1.6 ml) was added dropwise at 0°C and stirred during 15-30 minutes at 0°C. The resultant mixture was stirred during 1H30 at room temperature and the precipitate, separated by filtration, was washed with ether and then air dried to give 5.22 g of the title compound (3c) as white solid.

Yield= 96%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.15 (s, 3H), 4.21(s, 3H), 8.15 (m, 4H).

Intermediate 3d: R2= methyl, R3= 4-acetylamino-phenyl 1,3,4-thiadiazolium, 5-(4-Acetylaminophenyl)-3-methyl-2-(methylthio)-trifluoromethanesulfonic acid

To a suspension of (2d) (4.3 mmol, 1.28 g) in dichloromethane (15 ml) was added trimethylsilyl trifluoromethane-sulfonate (12.9 mmol, 2.34 mL) dropwise. The resulting mixture was stirred overnight. The precipitate was isolated by filtration and then dried under reduced pressure to give 1.3 g of the expected 3-methyl-2-methylthio[1,3,4]thiadiazolium triflate (3d) as a white solid.

Yield= 72%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.10 (s, 3H), 3.10 (s, 3H), 4.15 (s, 3H), 7.80 (dd, 2H), 7.95 (dd, 2H), 10.40 (s, 1H).

Intermediate 3e: R2= methyl, R3= 4-acetylamino-3-pyridyl 1,3,4-thiadiazolium, 5-(6-acetylamino-pyridin-3-yl)-3-methyl-2-(methylthio)-perchlorate

To a suspension of (2e) (3.4 mmol, 1 g) in ether (11 ml) was slowly added acetic anhydride (2 ml) followed by $HClO_4$ 70% (4 mmol, 0.7 g) dropwise at 0°C over 1 hour. The resulting mixture was then allowed to warm up to room temperature and stirred overnight. Additional $HClO_4$ 70% (0.7 mmol, 0.1g) was

added at 0°C and the mixture was stirred for 2h. The precipitate was isolated by filtration washed with AcOEt then dried under reduced pressure to give 1 g of the expected (3e).

Yield = 77%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.15 (s, 3H), 3.15 (s, 3H), 4.20 (s, 3H), 8.30 (dd, 1H), 8.40 (dd, 2H), 8.90 (d, H), 11.05 (s, 1H).

MS (m/z) / M+1 = 280.92

Compound I : PROTOCOL A

Example I1: R1= 3-benzoic acid, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

To a suspension of 1,3,4-thiadiazolium perchlorate (3a) (0.7 mmol, 0.25 g) in ethanol (3.5 ml), 3-aminobenzoic acid (1.05 mmol, 0.144 g) and triethylamine (0,7 mmol, 0.098 ml) were added, and the mixture was maintained at 70°C for 7 hours. On cooling to RT overnight, the solid formed was isolated by filtration to give 0.180 g of the expected compound.

Yield= 74.3%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.72 (s, 3H), 7.30 (dd, 1H), 7.5 (dd, 1H), 7.54 (dd, 2H), 7.60 (s, 1H), 7.54 (dd, 1H), 7.71 (dd, 2H), 12.91-13.04 (b, 1H).

MS (m/z) / M+1= 346/348

HPLC (uv purity, λ= 214 nm)= 99.03%

The following compounds were prepared by the procedure described in example I.1 using appropriate intermediates and reagents. The desired products were obtained after purification by chromatography on silica gel.

I1.1	(1R*,2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz 1-2-ylideneamino]-cyclohexanecarboxylic acid

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I1.2	(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol
I1.3	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz 1-2-ylidene]-(3-ethyl-phenyl)-amine
I1.4	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-pyrrolidin-3-yl-amine
I1.5	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-N',N'-dimethyl-benzene-1,4-diamine
I1.6	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-6-methyl-benzoic acid
I1.7	2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol
I1.8	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-ethyl-phenyl)-amine
I1.9	{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol

Example I1.10: R1= 3-carboxylic acid cyclohexyl, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid

Compound I1.10 was prepared by the procedure described in example I1 (3h at 75°C) using appropriate intermediates and reagents (protocol A).

The mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by silica gel chromatography eluting with dichloromethane containing from 0 to 5% of methanol and then isocratic elution with DCM / MeOH (90/10).

Yield= 7.0%

^{1}H-NMR (400MHz, DMSO) δppm: 0.95-1.20 (m, 4H), 1.62-1.74 (m, 3H), 1.74-1.80 (m 1H), 2.10-2.13 (b, 1H), 2.39-2.48 (b, 1H), 2.84-2.90 (m, 1H), 3.10 (3H, s), 7.33 (dd, 2H), 7.44 (dd, 2H), 11.89-11.84 (b, 1H).

MS (m/z) / M+1 = 352/354

HPLC (uv purity, λ= 214 nm)= 97.61%

Example I2: R1= 2-benzoic acid, R2= methyl, R3= 4-chloro-phenyl

2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

To a suspension of 1,3,4-thiadiazolium perchlorate (3a) (0.7 mmol, 0.25 g) in ethanol (3 ml), 2-aminobenzoic acid (0.84 mmol, 0.115 g) and triethylamine (0.7 mmol, 0.098 ml) were added, and the mixture was heated at 70°C for 7 hours. On cooling, the solid formed was filtered off to give 210 mg of the expected compound.

Yield= 87%

^{1}H-NMR (400MHz, DMSO)δ ppm: 3.8 (s, 3H), 7.20 (m, 1H), 7.2.8 (dd, 1H), 7.56-7.64 (m, 3H), 7.78 (dd, 2H), 7.95 (dd, 1H), 13.52-13.59 (b, 1H).

MS (m/z) / M+1= 346/348

HPLC (uv purity, λ= 214 nm)= 97.64%

Example I2.1: R1= (4-fluoro)-3 benzoic acid, R2= methyl, R3= 4-chloro-phenyl

5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid

Compound I2.1 was prepared by the procedure described in example I2 using appropriate intermediates and reagents(protocol A).

The precipitate obtained on cooling was washed with EtOH to give 0.250 g of the title compound.

Yield= 60%

^{1}H-NMR (400MHz, DMSO) δppm: 3.71 (s, 3H), 7.29-7.33 (m, 3H), 7.48-7.51(m 1H), 7.54 (dd, 2H), 7.70 (dd, 2H), 13.27-13.29 (b, 1H).

MS (m/z) / M+1= 364/366

HPLC (uv purity, λ= 214 nm)= 95.77%

Example I2.2: R1= (2,4,5-fluoro)-3 benzoic acid, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid

Compound I2.2 was prepared by the procedure described in example I2 using the appropriate intermediates and reagents. Acetonitrile was used as solvent and the reaction was warmed at 80°c for 24h (protocol A).
The solid formed after cooling was filtered off and washed with MeOH to give 0.250 g of the title compound.
Yield= 48.6%
^{1}H-NMR (400MHz, DMSO) δppm: 3.74 (s, 3H), 7.44-7.54 (m, 1H), 7.55 (dd, 2H), 7.73 (dd, 2H), 14.15-14.30 (b, 1H).
MS (m/z) / M+1= 400/402
HPLC (uv purity, λ= 214 nm)= 95.82%

Example I3: R1= propyl, R2= methyl, R3= 4-chloro-phenyl

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-propyl-amine

To a suspension of 1,3,4-thiadiazolium perchlorate (3a) (0.28 mmol, 0.10 g) in methanol (4 ml), propylamine (1.35 mmol, 0.115 ml) and triethylamine (0.28 mmol, 0.038 ml) were added, and the reaction was heated at 55°C for 5 hours. On cooling, the mixture was evaporated to dryness and the crude was chromatographed on silica gel (Alltech column, 2 g silica) with a mixture of cyclohexane:EtOAc (98:2) to give the expected compound.
Yield= 0.03g, 45.2%.
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.89 (t, 3H), 5.53-5.65 (m, 2H), 2.97 (t, 2H), 7.49 (dd, 2H), 7.62 (dd, 2H).
MS (m/z) / M+1= 268/270
HPLC (uv purity, λ= 214 nm)= 97.60%

The following compounds were prepared by the procedure described in example I3 using appropriate intermediates and reagents.

I3.1	(*S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol
I3.2	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiaz 1-2-ylidene]-[3-(4-methyl-piperazin-1-yl)-propyl]-amine
I3.3	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine
I3.4	3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one
I3.5	(4-Chloro-benzyl)-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine
I3.6	Benzyl-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine
I3.7	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine
I3.8	[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine
I3.9	(*S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-phenyl-propan-1-ol
I3.10	(*S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol

The following compounds were prepared by the procedure described in example I3 using appropriate intermediates and reagents and with isopropanol as solvent.

I3.11	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol
I3.12	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxymethyl-propane-1,3-diol
I3.13	tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz 1-2-ylidene]-amine
I3.14	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-

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	2-ylidene]-isopropyl-amine
I3.15	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
I3.16	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine
I3.17	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I3.18	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine
I3.19	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine
I3.20	N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine
I3.21	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3,4-dichloro-phenyl)-amine
I3.22	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-methoxy-phenyl)-amine
I3.23	(1R*,2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
I3.24	N'-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-N,N-dimethyl-ethane-1,2-diamine

Example I3.25: R1= (1R*, 2S*)-cyclohexyl-2-ol, R2= methyl, R3= 4-chloro-phenyl

(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

The compound I3.25 was prepared by the procedure described in example I3 (protocol A) with isopropanol as solvent.

The title product was isolated by chromatography on silica gel (Alltech, 2g silica) eluting with dichloromethane containing from 0 to 1% methanol.

Yield= 0.015 g, 12%

^{1}H-NMR (400MHz, DMSO) δppm: 1.20-1.30 (b, 2H), 1.40-1.50 (b, 2H), 1.50-1.72 (b, 4H), 2.80-2.83 (b, 1H), 3.50 (s, 3H), 3.55-3.60 (b, 1H), 4.02-4.04 (b, 1H), 7.45 (d, 2H), 7.60 (d,

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2H).
MS (m/z) / M+1= 324/3256
HPLC (uv purity, λ= 214 nm)= 96.62%

The following compound was prepared by the procedure described in example I3 with isopropanol as solvent.

I3.26	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine

Example I4: R1= 3-benzoic acid, R2= methyl, R3= 4-(methanesulfonyl)-phenyl

3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

To a suspension of 1,3,4-thiadiazolium perchlorate (3b) (0.547 mmol, 0.22 g) in ethanol (2.5 ml), 3-aminobenz ic acid (0547 mmol, 0.075 g) and triethylamine (0.601 mmol, 0.084 ml) were added, and the reaction was maintained f r 6 hours at 75°C. On cooling overnight, the precipitate was filtered off, washed with ethanol then purified on silica gel, eluted with a gradient of DCM then DCM:MeOH (95:5) t give 70 mg of the expected compound.
Yield= 33%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.78 (s, 3H), 7.31 (dd, 1H), 7.54 (dd, 1H), 7.60 (s, 1H), 7.65 (s, 1H), 7.97 (dd, 2H), 8.03 (dd, 2H), 12.92-12.03 (b, 1H).
MS (m/z) / M+1= 390
HPLC (uv purity, λ= 214 nm)= 95.14%

The following compounds were prepared by the procedure described in example I4 with an excess of triethylamine (10eq) and of the appropriate amine (10eq). The reaction was refluxed for 5h.

I4.1	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclopropyl-amine
I4.2	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-

	2-ylidene]-cyclohexylmethyl-amine

Example I5: R1= 3-hydroxyphenyl, R2= methyl, R3= 4-chlorophenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol

In this example, polystyrene morpholine resin was used t replace triethylamine and the isocyanate resin to remove the remaining amino derivative.

The suspension of morpholine resin (0.70 mmol, 0.20 g) and 3-aminophenol (0.84 mmol, 0.09 g) in ethanol (3.5 ml) was stirred at RT for 5 min before the addition of 1,3,4-thiadiazolium perchlorate (3a) (0.70 mmol, 0.25 g). After 5 hours at 70°C, the mixture was allowed to cool down before the filtration of the resin. The crude obtained after the evaporation of the solvent was purified on chromatography gel (Alltech column, 2 g silica) and eluted with gradient f DCM and MeOH:DCM (99:1) to give a mixture (0.07 g) of the remained amino derivative and the expected compound. To this mixture in DCM (7 ml) / MeOH (0.5 ml), was added the isocyanate resin (2.44 mmol, 2.00 g) and the suspension was stirred at RT overnight. After filtration of the resin, the filtrate was evaporated to dryness to give 30 mg of the pure product.

Yield= 13.5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.68 (s, 3H), 6.45-6.51 (m, 3H), 7.13-7.19 (m, 1H), 7.55 (dd, 2H), 7.71 (dd, 2H), 9.40-9.48 (b, 1H).

MS (m/z) / M+1= 318/320

HPLC (uv purity, λ = 214 nm)= 98.44%

Example I6: R1= 4-hydroxy-3-benzoic acid, R2= methyl, R3= 4-chlorophenyl

5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid

The compound I6 was prepared by the procedure described in example I2 (protocol A). The precipitate obtained on co ling

was washed with DCM then purified by chromatography n silica gel (Alltech column, 5g silica) eluted with a mixture of DCM/MeOH from 100/0 to 85/15.

Yield= 17.0%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.07 (s, 1H), 3.59 (s, 3H), 6.70 (d, 1H), 6.93-6.98 (m 1H), 7.30 (s, 1H), 7.38-7.41 (m, 2H), 7.57-7.62 (m, 2H).

MS (m/z) / M+1= 362/364

HPLC (uv purity, λ= 214 nm)= 95.89%

The following compounds were prepared by the procedure described in example I6, using appropriate intermediates and reagents. Either morpholine resin or pyridine was used t replace triethylamine.

I6.1	(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.2	4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-diethylaminomethyl-phenol
I6.3	2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol
I6.4	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(2-ethyl-phenyl)-amine
I6.5	(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol
I6.6	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-methoxy-phenyl)-amine
I6.7	[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylidene]-(3-fluoro-phenyl)-amine
I6.8	(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I6.9	{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid
I6.10	N-[5-(4-Chl ro-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylidene]-N',N'-dimethyl-benzene-

	1,3-diamine
I6.11	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide

Example I7: R1= Exo-2-norbornyl, R2= methyl, R3= 4-chloro-phenyl

Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

The compound I7 was prepared by the procedure described in example I3 using appropriate intermediates and reagents (protocol A).

The title product was isolated by chromatography on silica gel (Alltech, 2g silica) with a gradient of cyclohexane: EtOAc from 100: 0 to 97:3

Yield= 44.8 %

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.09-1.18 (b, 3H), 1.27-1.33 (b, 1H), 1.40-1.52 (b, 2H), 1.58-1.62 (m, 1H), 1.70-1.76 (m, 1H), 1.99-2.10 (b, 1H), 2.24-2.27 (b, 1H), 3.45 (s, 3H), 7.53 (d, 2H) 7.64 (d, 2H).

MS (m/z) / M+1= 320/322

HPLC (uv purity, λ= 214 nm)= 93.17%

Example I8: R1= (1R*, 2R*)-cyclohexyl-2-ol, R2= methyl, R3= 4-chloro-phenyl

(1R*,2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol

The compound I8 was prepared by the procedure described in example I3 using appropriate intermediates and reagents (protocol A).

Triethylamine was replaced by morpholine resin (2.1 mmol, 0.61 g, loading 3.47 mmol/g); the mixture of morpholine resin and trans-2-aminocyclohexanol hydrochloride (2.1 mmol, 0.318 g) was stirred in ethanol (3.5 ml) at RT for 5 min before the addition of 3-methyl-2-methylthio[1,3,4]thiadiazolium perchlorate (3a) (0.7 mmol, 0.25 g). The residue was subjected t silica gel chromatography (Alltech c lumn, 2g silica) eluting with

dichloromethane containing from 0 t 1% methanol.
Yield= 0.050g, 22%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.25 (m, 4H), 1.50-1.66 (m, 3H), 1.71-1.79 (b, 1H), 2.28-2.33 (m, 1H), 3.21-3.27 (m, 1H), 3.40 (s, 3H), 4.38 (s, 1H), 7.42 (dd, 2H), 7.54 (dd, 2H).
MS (m/z) / M+1= 324/326
HPLC (uv purity, λ= 214 nm)= 99.9%

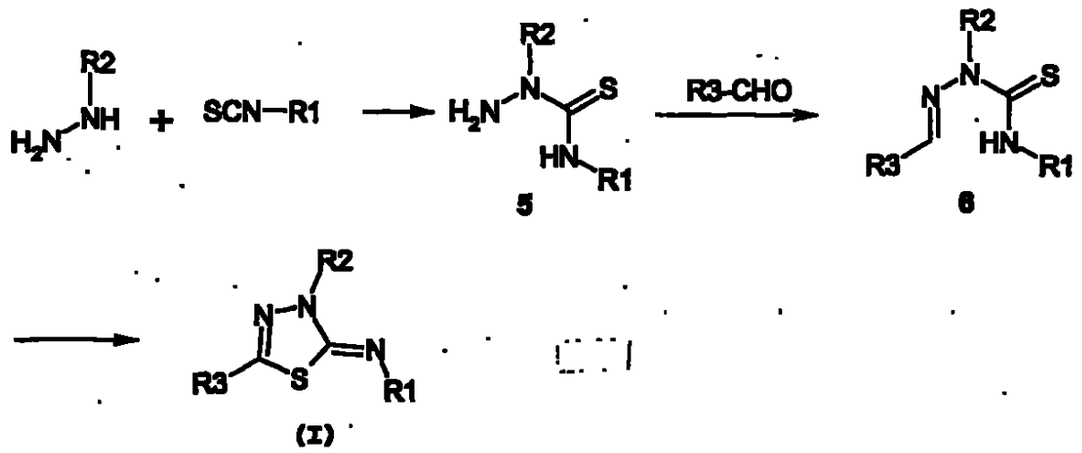
The following compounds were prepared by the procedure described in example I8 using appropriate intermediates and reagents.

I8.1	5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol
I8.2	3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid
I8.3	3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid
I8.4	(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine

Example I9: R1= (1R*, 2R*)-cyclohexyl-2-ol, R2= methyl, R3= 4-(methanesulfonyl)-phenyl
(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol
The compound I9 was prepared by the procedure described in example I4 (protocol A).
3-methyl-2-methylthio[1,3,4]thiadiazolium perchlorate (3b) (0.372 mmol, 0.15 g), trans-2-aminocyclohexanol hydrochloride (0.410 mmol, 0.062 g) and triethylamine (0.7814 mmol, 0.109 ml) were reacted in ethanol (1.5 ml). The crude was twice chromatographed on silica gel with a mixture of DCM: MeOH (98:2) to give the title product.
Yield= 0.030g, 23%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.37 (m, 5H), 1.60-1.78

(b, 3H),1.81-1.90 (b, 1H), 3.3 (s, 3H), 3.32-3.40 (b, 1H), 3.52 (s, 3H), 4.53 (s, 1H), 7.89 (d, 2H), 8.01 (d, 2H).
MS (m/z) / M+1= 368/370
HPLC (uv purity, λ= 214 nm)= 99.17%

Protocol B



Intermediate 5 : PROTOCOL B

Intermediate 5a: R1= cyclohexyl, R2= methyl
Hydrazinecarbothioamide, N-(cyclohexyl)-1-methyl
The requisite cyclohexylisothiocyanate,(70.8 mmol, 10 g) was dissolved in methanol (35 ml) and this solution was added dropwise (30 min) to a stirred solution of methylhydrazine (134.5 mmol, 7 ml) in water (35 ml) at 0°C. After mixing, the solution was allowed to stir at RT overnight. The precipitate was removed by filtration. The solid was washed with cold EtOH to give 11.7 g of the expected derivative 5a.
Yield : 88.7%
^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.25 (m,5H), 1.50-1.60 (m,1H), 1.60-1.70 (m,2H), 1.80-1.90(m,2H), 3.40 (s,3H), 3.90-4.00 (m,1H), 4.80(s,2H), 7.85 (d,1H).
MS (m/z) / M+1 = 188,33

Intermediate 5b: R1= cyclohexyl, R2= H
Hydrazinecarbothioamide, N-cyclohexyl
The requisite cyclohexylisothiocyanate, (141 mmol, 20 ml)

was dissolved in methanol (30 ml) and this solution was added dropwise (35 min) to a stirred solution of hydrazinehydrate (423 mmol, 13.2 ml) in methanol (200 ml) at 0°C. After mixing, the solution was allowed to stir at RT overnight. The precipitate was removed by filtration. The solid was washed with cold EtOH to give 14.9 g of the expected derivative (5b).

Yield: 61%

^{1}H-NMR(400MHz , DMSO) δ ppm : 1.10-1.35(m,5H), 1.50-1.60 (m,1H), 1.60-1.75(m,2H), 1:75-1.90 (m,2H), 4.00-4.10 (m,1H), 4.40 (s,2H), 7.50 (d,1H), 8.50 (s,1H).

MS (m/z) / M+1 =174,25

Intermediate 5c: R1= 3-benzoic-acid-methyl-ester, R2= H

Hydrazinecarbothioamide,N-(3-benzoic-acid-methyl-ester)

3-methoxycarbonylisothiocyanate(77.6 mmol, 15 g) was added dropwise (30 min) to a stirred solution of hydrazine hydrate (97 mmol, 4.7 mL) in methanol (40 mL) at -10°C. After stiring at -10°C for 5h, the solution was allowed to stir at room temperature overnight. The precipitate was filtered and washed with cold methanol to give 15.4 g of the expected compound (yield: 88%).

^{1}H-NMR (400 MHz , DMSO) δ ppm: 3.85 (s, 3H), 4.85 (brs, 1H), 7.43(t, 1H), 7.68 (d, 1H), 7.87 (d, 1H), 8.33 (s, 1H), 9.23 (s, 1H).

MS (m/z) / M+1 = 226

Intermediate 6: PROTOCOL B

Intermediate 6a: R1=cyclohexyl, R2=methyl , R3= 2,4-dichlorophenyl

Hydrazinecarbothioamide, N-cyclohexyl-2-[(2,4-chlorophenyl)methylene]

A suspension of 2-methylthiosemicarbazide (5a) (2.67 mmol, 500 mg)in ethanol (5 ml) and 2,4-dichlorobenzaldehyde (2.94 mmol, 515 mg) were heated at 75°C for 18 hours. After cooling, the formed precipitate was filtered and washed with cold ethanol to give 876 mg of the title compound.

Yield: 95.3%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.25 (m, 1H), 1.25-1.35 (m, 2H), 1.35-1.55 (m, 2H), 1.60-1.70 (m, 1H), 1.70-1.80 (m, 1H), 1.90-2.00 (m, 2H), 3.80 (s, 3H), 4.10-4.30 (m, 1H), 7.50 (d, 1H), 7.70 (s, 1H), 8.00 (s, 1H), 8.20 (d, 1H), 8.50 (d, 1H).

EXAMPLE I : PROTOCOL B

Example I10: R1= cyclohexyl, R2= methyl, R3= 2,4-dichlorophenyl

Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

The appropriate thiosemicarbazone (prepared by the procedure described in example 6a) (2.3 mmol, 800 mg) was suspended in ethanol (5ml) and the oxidant $FeCl_3$,$6H_2O$ (5.06 mmol, 1.38 g) dissolved in ethanol (5 ml) was added. The mixture was heated at 75°C during 19h (TLC control). The oxidant (1.15 mmol, 0.31 g) was added to allow reaction to completion. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a residue which was chromatographed on silica gel column (using a gradient of solvent ethyl acetate-cyclohexane starting with a ratio 5/95) to isolate 230 mg of the pure thiadiazoline. The byproduct mainly formed during this reaction is the 1,2,4-triazoline-5-thione.

Yield: 35%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.55-2.70 (m, 1H), 3.50 (s, 3H), 7.50 (d, 1H), 7.70-7.80 (m, 2H)

MS (m/z) / M+1= 344.1

HPLC (uv purity, λ= 214 nm): 99,9%

Example I10.1 : R1= cyclohexyl, R2= methyl, R3= 2-chloro-

phenyl

[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Compound I10.1 was prepared by the procedure described in I10 using appropriate intermediates and reagent.

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 6% AcOEt.

Yield: 6%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.70 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 7.40-7.50 (m, 2H), 7.60 (d, 1H), 7.70 (d, 1H)

MS (m/z) / M+1= 310.2

HPLC (uv purity, λ= 214 nm): 99.9%

Example I11: R1= cyclohexyl, R2= methyl, R3= 4-(trifluoromethyl)-phenyl

Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

The appropriate thiosemicarbazone (prepared by the procedure described in example 6a) (2 mmol, 700 mg) was suspended in ethanol (5 ml) and the oxidant $FeCl_3$, $6H_2O$ (4.4 mmol, 1.21 g) dissolved in ethanol (5 mL) was added. The mixture was heated at 75°C during 19h. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a residue which was chromatographed on silica gel column (using a gradient of solvent ethyl acetate-cyclohexane as eluent with a rapport 5/95) to isolate 290 mg the pure thiadiazoline.

Yield:42%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.25-1.50 (m, 5H), 1.60-1.70 (m, 1H), 1.75-1.90 (m, 4H), 2.65-2.75 (m, 1H), 3.60 (s, 3H), 7.85-7.95 (m, 4H)

MS (m/z) / M+1= 342.6.

HPLC (uv purity, λ= 214 nm): 99.9%

Example I12: R1= cyclohexyl, R2= methyl, R3= 4-pyridyl

Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Compound I12 was prepared by the procedure described in example I11 using appropriate intermediates and reagents (protocol B).

The mixture was concentrated by distillation under reduced pressure and the residue was dissolved in water. The aqueous mixture was then basified with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated solution of NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography (eluent: cyclohexane/ethyl acetate, 95/5).

Yield: 80%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.55 (s, 3H), 7.60 (d, 2H), 8.65 (d, 2H)

MS (m/z) / M+1= 275.2

HPLC (uv purity, λ= 214 nm): 99.9%

Example I13: R1= cyclohexyl, R2= methyl, R3= 3-chloro-phenyl

[5-(3-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Compounds I13 was prepared by the procedure described in example I10 using appropriate intermediates and reagents (protocol B).

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 6% AcOEt.

Yield: 23%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.50 (s, 3H), 7.45-7.55 (m, 2H), 7.55-7.65 (m, 1H), 7.70 (s, 1H)

MS (m/z) / M+1= 308

HPLC (uv purity, λ= 214 nm): 99.9%

Example I14: R1= cyclohexyl, R2= methyl, R3= 4-cyano-phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-benzonitrile

Compounds I14 was prepared by the procedure described in example I10 using appropriate intermediates and reagents (protocol B).

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 8% AcOEt.

Yield: 10%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.80 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.80 (d, 2H), 7.90 (d, 2H)

MS (m/z) / M+1= 299.2

HPLC (uv purity, λ= 214 nm): 99.3%

Example I15 : R1= cyclohexyl, R2= methyl, R3= 4-methylsulfonyl-phenyl
Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compounds I15 was prepared by the procedure described in example I10 using appropriate intermediates and reagents (protocol B).

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 10% AcOEt.

Protocol D gave better yield to prepare I15.

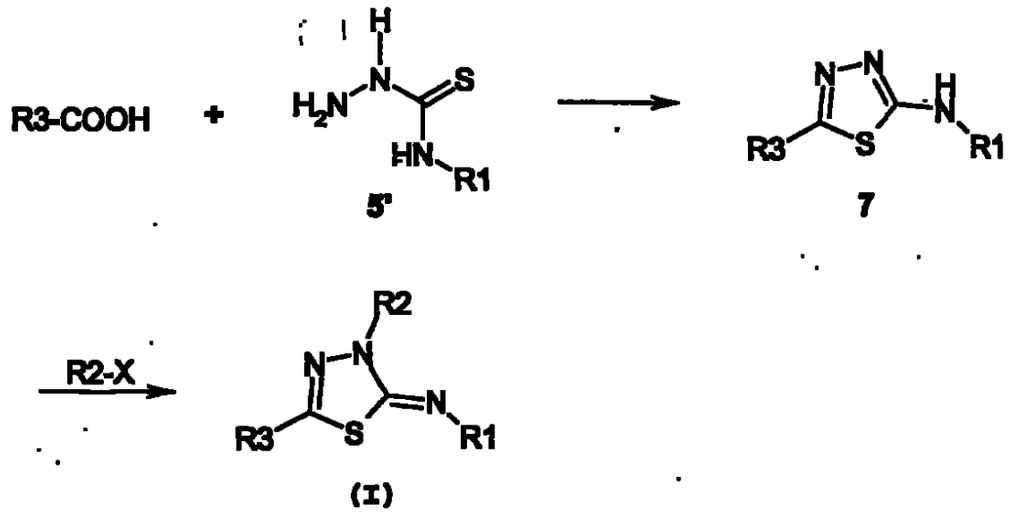
Yield: 3%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.45-1.55 (m, 1H), 1.60-1.75 (m, 4H), 2.50-2.60 (m, 1H), 3.20 (s, 3H), 3.45 (s, 3H), 7.80 (d, 2H), 7.90 (d, 2H).

MS (m/z) / M+1= 352.5

HPLC (uv purity, λ= 214 nm): 87.3%

Protocol C



Intermediate 7: PROTOCOL C

Intermediate 7a: R1= cyclohexyl, R3= 4-chloro-3-sulfamoyl-phenyl

2-Chloro-5-(5-cyclohexylamino-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a mixture of 4-chloro-3-sulfamoyl-benzoic acid (6.36 mmol, 1.5 g), thiosemicarbazide (5b) (6.36 mmol, 1.10 g) in dioxane (40 ml) at 60°C, $POCl_3$ (6.36 mmol, 600 µl) was added and the mixture was warmed at reflux for 2h30 and 16h at RT. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with a solution of diluted NH_4OH. The yellow precipitate obtained was collected by filtration, washed with water before drying under vacuum over P_2O_5 to give 2g of the desired product.
Yield = 84 % ;

^1H (400MHz, DMSO) δ ppm : 1.10-1.37 (m, 5H), 1.55 (m, 1H), 1.70 (m, 2H), 1.98 (m, 2H), 3.55 (m, 1H), 7.66-7.82 (m, 3H), 7.90 (m, 1H) ; 8.25-8.37 (br, 2H).
MS (m/z) / M+1 = 373/375

Intermediate 7b: R1= cyclohexyl, R3= 2,4-dichloro-5-sulfamoyl-phenyl

2,4-Dichl ro-5-(5-cyclohexylamino-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a mixture of 2,4-dichlorobenzoic acid (1.85 mmol, 500 mg), thiosemicarbazide (5b) (1.85 mmol, 320 mg) in anhydrous dioxane (10 mL) at 70-80°C, $POCl_3$ (1.85 mmol, 173 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration, washed with water and purified by silica gel chromatography using cyclohexane/ethyl acetate as eluent to give 351mg of the title compound.

Yield: 46.3%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.65 (m, 1H), 1.65-1.80 (m, 2H), 1.90-2.05 (m, 2H), 3.50-3.70 (m, 1H),7.85 (d, 2H), 8.05 (s, 1H), 8.20-8.40 (m, 1H), 8.60 (s, 1H).

MS (m/z) / M+1= 407.1

HPLC (uv purity, λ= 214 nm): 97.1%

Intermediate 7c: R1= cyclohexyl, R3= 3-thienyl

Cyclohexyl-(5-thiophen-3-yl-[1,3,4]thiadiazol-2-yl)-amine.

To a mixture of 3-thiophenecarboxylic acid (3.9 mmol, 500 mg), thiosemicarbazide 5b (3.9 mmol, 675 mg) in anhydrous dioxane (10 ml) at 60-65°C, $POCl_3$ (5 mmol, 473 µl) was added and the mixture was warmed at 95°C for 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration and washed with water. The solid was then dried under vacuum to provide 965 mg of the desired compound (7c).

Yield : 93%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75(m, 2H), 1.90-2.00 (m, 2H), 3.45-3.55 (m, 1H), 7.45 (d, 1H), 7.65 (d, 1H),7.80 (d, 1H), 7.85 (s, 1H).

Intermediate 7d: R1= cyclohexyl, R3= 3-chloro-2,6-dimethoxyphenyl

[5-(3-Chloro-2,6-dimethoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

To a mixture of 3-chloro-2,6-dimethoxybenzoic acid (2.3 mmol, 500 mg), thiosemicarbazide 5b (2.3 mmol, 399 mg) in anhydrous dioxane (10 ml) at 70-80°C, $POCl_3$ (2.3 mmol, 215 µl) was added and the mixture was warmed at 95°C f r 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration, washed with water and dried under vacuum. The solid was subjected to flash chromatography eluting with ethyl acetate/cyclohexane t give 115 mg of the title compound.

Yield: 14%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.80 (m, 2H), 1.95-2.05 (m, 2H), 3.50-3.60 (m, 1H), 3.70 (s, 3H), 3.80 (s, 3H), 7.00 (d, 1H), 7.55 (d, 1H), 7.75(d, 1H).

MS (m/z) / M+1 = 354.1

Intermediate 7e: R1= cyclohexyl, R3= 3-bromo-4-methoxyphenyl

[5-(3-Bromo-4-methoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

To a mixture of 3-bromo-4-methoxybenzoic acid (2.16 mmol, 500 mg), thiosemicarbazide 5b (2.16 mmol, 375 mg) in anhydrous dioxane (10 ml) at 60-65°C, $POCl_3$ (2.8 mmol, 262 µl) was added and the mixture was warmed at 95°C f r 5 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration, washed with water and dried under vacuum. The solid was solubilized in 50 ml f dichloromethane/methanol (7/3) to which was additionned a morpholine resin (13.88 mmol, 4 g). The mixture was stirred overnight to remove the excess of acid. The resin morpholine salt was filtered and the rganic layer was concentrated by distillation under reduced pressure to give 740 mg of the

purified product (7e).
Yield: 92.8%
^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 2H), 1.90-2.00 (m, 2H), 3.45-3.55(m, 1H), 7.45 (dd, 1H), 7.65 (dd, 1H), 7.80 (dd, 1H), 7.85 (dd, 1H).

Intermediate 7f: R1= cyclohexyl, R3= 2-pyrazinyl
Cyclohexyl-(5-pyrazin-2-yl-[1,3,4]thiadiazol-2-yl)-amine
To a mixture of 2-pyrazine carboxylic acid (2.885 mmol, 0.358 g), thiosemicarbazide (5b) (2.885 mmol, 0.5 g) in anhydrous dioxane (10 ml), was added phosphorus oxychloride (3.751 mmol, 0.350 ml) at 90°C and the mixture was heated at 95°C for 5 hours. The mixture was then basified to pH 7 with a saturated solution of sodium bicarbonate then extracted with EtOAc. The organic phase was dried over $MgSO_4$ and evaporated to dryness to give the expected product.
Yield= 0.6 g, 79.6%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.44 (m, 5H), 1.56-1.63 (b, 1H), 1.70-1.77 (b, 2H), 2.00-2.05 (b, 2H), 3.60-3.68 (b, 1H), 8.22 (d, 1H), 8.67-8.69 (m, 2H), 9.28 (s, 1H).

Intermediate 7g: R1= cyclohexyl, R3 =3,4-dihydroxyphenyl
4-(5-Cyclohexylamino-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol
To a mixture of 3,4-dihydroxybenzoic acid (2.885 mmol, 0.445 g), thiosemicarbazide (5b) (2.885 mmol, 0.500 g) in anhydrous dioxane (10 ml), was added phosphorus oxychloride (3.751 mmol, 0.350 ml) at 90°C and the mixture was heated at 95°C for 5 hours. The mixture was basified with a saturated solution of sodium bicarbonate to pH 7 then stirred at RT overnight. The precipitate was filtered, washed with hexane then dried to give the title compound.
Yield: 71%
^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.39 (m, 5H), 1.55-1.62 (b, 1H), 1.70-1.78 (b, 2H), 1.95-2.00 (b, 2H), 3.48-3.53 (b, 1H), 6.80 (d, 1H), 6.98 (d, 1H), 7.19 (s, 1H), 7.68 (d, 1H), 9.20-9.40 (b, 2H).

Intermediate 7h: R1 = cyclohexyl, R3= 4-chloro-phenyl

[5-(4-Chloro-phenyl)-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

Thiosemicarbazone (6b) (obtained from 5b following the protocol 6a) (10 mmol, 3 g) was suspended in ethanol (50 ml) and the oxidant $FeCl_3,6H_2O$ (23 mmol, 6.3 g) was added. The mixture was heated at reflux for 3h. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The organic layer was washed with water, dried under magnesium sulphate, filtered, and distilled to give a residue submitted t another oxidative process with $FeCl_3$, $6H_2O$ (3 g) in ethanol (50 ml). The mixture was heated at reflux for 3h and 12h at RT. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a residue which was triturated and wash with cyclohexane to give 2.5g of the title product.

Yield: 85%

^{1}H-NMR (400MHz, DMSO) δ ppm: 0.95-1.22 (m, 5H), 1.35-1.45 (b, 1H), 1.50-1.60 (m, 2H), 1.80-1.87 (m, 2H), 3.32-3.42 (b, 1H), 7.35 (d, 2H), 7.55 (d, 2H), 7.75 (d, 1H)

MS (m/z) / M+1 = 294.1

HPLC (uv purity, λ= 214 nm): 97.21%

Intermediate 7i: R1= cyclohexyl, R3= 3-chloro-4-hydroxy-5-methoxyphenyl

2-chloro-4-(5-cyclohexylamino-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol

To a mixture of 3-chloro-4-hydroxy-5-methoxybenzoic acid (2.468 mmol, 500 g), thiosemicarbazide (5b) (2.468 mmol, 427 mg) in dioxane (10 ml) at 65°C, $POCl_3$ (3.2 mmol, 300 µl) was added and the mixture was warmed at 95°C for 3h30. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with a s lution of diluted NH_4OH. The precipitate obtained was collected by

filtration, washed with water bef re drying under vacuum over P_2O_5 to give 675 mg of the desired product.
Yield = 80%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.36 (m, 5H), 1.53-1.63 (m, 1H), 1.67-1.80 (m, 2H), 1.95-2.05 (m, 2H), 3.45-3.57 (m, 1H), 3.90 (s, 3H), 7.25 (s, 1H) ; 7.30 (s, 1H), 7.85 (d, 1H), 9.90 (s, 1H)

Intermediate 7j: R1= 3-benzoic-acid-methyl-ester, R3= 3-cyano-phenyl

3-[5-(3-Cyano-phenyl)-[1,3,4]thiadiazol-2-ylamino]-benzoic acid methyl ester

To a mixture of 3-cyanobenzoic acid (2.92 mmol, 0.43 g), (5c) (3 mmol, 0.7 g) in dioxane (10 mL) at 85°C, $POCl_3$ (3.8 mmol, 350 µL) was added and the mixture was heated at 95°C for 3h30. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with an aqueous saturated solution of $NaHCO_3$. The precipitate obtained was collected by filtration, washed successively with water and with ether before being dried under vacuum to give 0.5 g of the desired product (yield: 49%).

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.88 (s, 3H), 7.53 (t, 1H), 7.63 (d, 1H), 7.72 (t, 1H), 7.86 (d, 1H), 7.96 (d, 1H), 8.23 (d, 1H), 8.32 (s, 1H), 8.43 (s, 1H), 10.89 (s, 1H).
MS (m/z) / M+1 = 337

Intermediate 7k: R1= 3-benzoic-acid-methyl-ester, R3= 2-pyridyl

3-(5-Pyridin-2-yl-[1,3,4]thiadiazol-2-ylamino)-benzoic acid methyl ester

To a mixture of picolinic acid (2.92 mmol, 0.36 g), (5c) (3 mmol, 0.7 g) in dioxane (10 ml) at 85°C, $POCl_3$ (3.8 mmol, 350 µL) was added and the mixture was heated at 95°C for 5h. The solvent was removed by distillation under reduced pressure t give a crude material. Methanol was added and the precipitate obtained was collected by filtration, washed with methanol and dried under vacuum t give 0.59 g (61%) of

the desired product. The crude material was engaged in the next step without purification.

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.5 (m, 2H), 7.6 (d, 1H), 7.88 (d, 1H), 7.98 (t, 1H), 8.12 (d, 1H), 8.42 (s, 1H), 8.63 (d, 1H), 10.9 (s, 1H).

MS (m/z) / M+1 = 313/314/315

EXAMPLE I : PROTOCOL C

Example I16: R1= cyclohexyl, R2= methyl, R3= 2,4-dichloro-5-sulfamoyl-phenyl

2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a solution of 1,3,4-thiadiazole 7b (0.195 mmol, 80 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (0.23 mmol, 27 µl) was added. The resultant mixture was stirred for 24 h. To this solution was added 0.527 mmol (64 µl) of methyltrifluoromethane sulfonate to allow reaction to completion, and 0.585 mmol (82 µl) of triethylamine. The filtrate is concentrated by distillation under reduced pressure. The product was purified via column chromatography on silica gel (eluted with cyclohexane/ethyl acetate, 80/20) to give 48 mg of the title product.

Yield: 58%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.80 (d, 2H), 8.0 (s, 1H), 8.35 (s, 1H).

MS (m/z) / M+1: 421.3

HPLC (uv purity, λ= 214 nm): 99.4%

Example I17: R1= cyclohexyl, R2= methyl, R3= 3-thienyl

Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4] thiadiazol-2-ylidene)-amine

To a solution of 1,3,4-thiadiazole 7c (0.75 mmol, 200 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (1.13 mmol, 128 µl) was added. The resultant mixture was stirred for 24 h. To this solution was added 0.225 mmol (26

µl) of methyltrifluoromethanesulfonate to allow reaction t completion, and 0.675 mmol (94 µl) of triethylamine. The mixture is concentrated by distillation under reduce pressure and the residue was dissolved in water. The aqueous mixture was then basified (pH= 5-6) with saturated $NaHCO_3$ solution with ethyl acetate. The organic layer was saturated with NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography, eluting with cyclohexane containing from 0 to 15% AcOEt to provide 80 mg of the desired product.
Yield : 38%
^{1}H-NMR (400MHz , DMSO): δ ppm= 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.7-1.8 (m, 4H), 2.55-2.65 (m, 1H), 3.45 (s, 3H), 7.40 (d, 1H), 7.70 (d, 1H), 7.85 (s, 1H).
MS (m/z) / M+1= 280.23
HPLC (uv purity, λ= 214 nm): 99.9%

Example I17.1: R1= cyclohexyl, R2= methyl, R3= 3,5-dichloro-phenyl

Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I17.1 was prepared by the procedure described in example I17 using appropriate intermediates and reagents.
Yield: 43%
^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.90 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 7.65 (s, 2H), 7.70 (s, 1H)
MS (m/z) / M+1= 342.2
HPLC (uv purity, λ= 214 nm): 99.9%

Compound I17.2 was prepared by the procedure described in example I17 using appropriate intermediates and reagents.

I17.2	Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Example I18: R1= cyclohexyl, R2= methyl, R3= 3-chloro-2,6-

dimethoxyphenyl.

[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of the 1,3,4-thiadiazole 7d (0.226 mmol, 80 mg) in anhydrous dioxane (10 mL), methyltrifluoro methanesulfonate (0.27 mmol, 31 µl) was added. The resultant mixture was stirred for 24 h. To this solution was added 0.068mmol (7 µl) of methyltrifluoromethanesulfonate to allow reaction to completion. The mixture was concentrated by distillation under reduced pressure and the residue was dissolved in water. The aqueous mixture was then basified (pH= 5-6) with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated solution of NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography. (eluent: cyclohexane/ethyl acetate, 80/20). 11 mg of desired product was obtained.

Yield: 13%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.50-2.60 (m, 1H), 3.50 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 7.00 (d, 1H), 7.60 (d, 1H)

MS (m/z) / M+1= 368.26

HPLC (uv purity, λ= 214 nm): 99.7%

Compound I18.1 was prepared by the procedure described in example I18 using appropriate intermediates and reagents:

I18.1	Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Example I18.2: R1= cyclohexyl, R2= methyl, R3= 2-(5-pyridin-2-yl)-thienyl

Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I18.2 was prepared by the procedure described in example I18 using appropriate intermediates and reagents. The residue was purified by silica gel chromatography

eluting with a gradient of cyclohexane containing from 0 t 10% ethyl acetate.

Yield: 57%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.35 (m, 5H), 1:50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.55-2.65 (m, 1H), 3.45 (s, 3H), 7.30 (m, 1H), 7.35 (d, 1H), 7.80 (d, 1H), 7.85 (m, 1H), 7.95 (d, 1H), 8.55 (d, 1H).

MS (m/z) / M+1= 357.3

HPLC (uv purity, λ= 214 nm): 99.5%

Example I18.3: R1= cyclohexyl, R2= methyl, R3= 3,5-dihydroxy-4-methoxy-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol, compound with trifluoro-methanesulfonic acid

Compound I18.3 was prepared from the appropriate 1,3,4-thiadiazole 7 prepared by the procedure described in example I18. In this particular case, the mixture was concentrated and the formed precipitate was filtered and washed with ethyl acetate to give the expected compound as a salt f trifluoromethansulfonic acid.

Yield: 45%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1-1.40 (m, 5H), 1.45-1.55 (m, 1H), 1.65-1.75 (m, 2H),1.85-1.95 (m, 2H), 3.05-3.20 (m, 1H), 3.6 (s, 3H), 4.00 (bs, 3H), 6.65 (s, 2H), 9.60 (bs, 2H), 10.00 (bs, 1H).

MS (m/z) / M+1= 336.4

HPLC (uv purity, λ= 214 nm): 99.7%

Example I18.4: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-4,5-dimethoxy-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadias 1-2-yl)-2,3-dimethoxy-phenol;compound with trifluoro-methanesulfonic acid

Compound I18.4 was prepared from the appropriate 1,3,4-thiadiazole 7 prepared by the procedure described example I18. In this particular case, the mixture was concentrated

and the formed precipitate was filtered and washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.
Yield: 11%
1H-NMR (400MHz , DMSO) δ ppm: 1.10-1.50 (m, 5H), 1.60-1.70 (m, 1H), 1.75-1.85 (m, 2H),1.95-2.10 (m, 2H), 3.10-3.25 (m, 1H), 3.75 (s, 3H), 3.85 (s, 6H), 6.85 (s, 1H), 6.95 (s, 1H), 9.80 (bs, 1H), 9.90 (bs, 1H).
MS (m/z) / M+1= 350.45
HPLC (uv purity, λ= 214 nm): 99.9%

Example I18.5: R1= cyclohexyl, R2= methyl, R3= 4-chloro-phenyl
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
Compound I18.5 was prepared by the procedure described in example I18 using appropriate intermediates and reagents.
^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.57-1.63 (m, 1H), 1.70-1.82 (m, 4H), 2.60 (br, 1H), 3.50 (s, 3H), 7.52(d, 2H), 7.65 (d, 2H).
MS (m/z) / M+1= 308/310
HPLC (uv putrity, λ= 214nm): 94.24%

Example I18.6: R1= cyclohexyl, R2= methyl, R3= 3-chloro-4-hydroxy-5-methoxy-phenyl
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid
Compound I18.6 was prepared from the appropriate 1,3,4-thiadiazole 7i.To a solution of intermediate 7i (2 mmol, 675 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (3 mmol, 337 µl) was added. The resultant mixture was stirred for 48 h to give a precipitate. The mixture was filtered and washed with ethyl acetate to give 400 mg of desired product as a salt f trifluoromethanesulfonic acid.
Yield: 40%
^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.55 (m, 5H), 1.60-1.70

(m, 1H), 1.76-1.88 (m, 2H), 2.00-2.11 (m, 2H), 3.11-3.25 (m, 1H), 3.85 (s, 3H), 3.95 (s, 3H), 7.30 (s, 1H), 7.48 (s, 1H), 9.90 (s, 1H), 10.50 (s, 1H).

MS (m/z) / M+1= 354/356

HPLC (uv purity, λ= 214 nm): 99.4%

Example I19: R1= cyclohexyl, R2= methyl, R3= 4-chloro-3-sulfamoyl-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

To a solution of 1,3,4-thiadiazole 7a (0.215 mmol, 80 mg) in anhydrous dioxane (10 mL), methyltrifluoromethane sulfonate (0.257 mmol, 29 µl) was added. The resultant mixture was stirred for 24 h. To this solution was added (0.065 mmol, 7 µl) of methyltrifluoromethanesulfonate to allow reaction to completion. The filtrate is concentrated by distillation under reduced pressure and the residue was dissolved in water. The aqueous mixture was then basified (pH= 5-6) with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with a saturated solution of NaCl and dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography. (eluted with a gradient of cyclohexane/ethyl acetate) to afford 59 mg of pure product.

Yield: 71%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.25-1.55 (m, 5H), 1.65-1.75 (m, 1H), 1.75-1.95 (m, 4H), 2.70-2.80 (m, 1H), 3.65 (s, 3H), 7.80-7.95 (m, 4H), 8.30 (dd, 1H).

MS (m/z) / M+1: 387.3

HPLC (uv purity, λ= 214 nm): 99.7%

Example I19.1: R1= cyclohexyl, R2= methyl, R3= 4-chloro- N,N-diethyl-3-sulfonamide-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadias 1-2-yl)-N,N-diethyl-benzenesulfonamide

To a mixture f compound I19 (0.258 mmol, 0.100 g), tetra-n-

butylammonium hydrogen sulphate (0.0258 mmol, 0.090 g), 50% aqueous sodium hydroxide (0.300 ml) and toluene (2.2 ml), was added ethylbromide (0.310 mmol, 0.023 ml). The reaction was stirred at RT for 2h and then heated to 90°C for 1h30 before a second addition of ethylbromide (0.310 mmol, 0.023 ml). The mixture was heated at 90°C for 2h30 and the volatiles were removed by distillation. The crude material was solubilized with ethyl acetate and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 0.1 g of the expected product as a white solid.

Yield= 87.7%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.00 (t, 6H), 1.10-1.32 (b, 5H), 1.48-1.54 (m, 1H), 1.65-1.73 (b, 4H), 2.53-2.62 (b, 1H), 3.20-3.30 (m, 4H), 3.48 (s, 3H), 7.68-7.79 (m, 2H), 8.11 (s, 1H).

MS (m/z) / M+1= 443/445

HPLC (uv purity, λ= 214 nm)= 99.72%

Example I19.2: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl {5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine

To a solution of I19 (0.516 mmol, 0.2 g) in DMF (13 ml) were added potassium carbonate (1.548 mmol, 0.214 g) and water (3 ml). The mixture was stirred at RT until obtaining an homogenous solution and then the bis-(2-chloro-ethyl)methyl-amine hydrochloride (0.516 mmol, 0.10 g) was added. After a day of stirring, the mixture was warmed at 80°C for 15h. The solvents were then evaporated and the crude material was solubilized in dicloromethane. The organic layer was washed with a satured solution of bicarbonate of sodium, then with brine. After fitration, the filtrate was dried over $MgSO_4$ and concentrated by distillation. The crude material was chromatographed on silica gel, eluting with dichloromethane containing from 0 to 5% methanol. The s lid product was then washed with ethyl acetate.

Yield= 10%
^{1}H-NMR (400MHz,$CDCl_3$ + D_2O) δ ppm: 1.20-1.48 (m, 5H), 1.62-1.68 (m, 1H), 1.79-1.89 (m, 4H), 2.45 (s, 3H), 2.45 (t, 4H), 2.55-2.65 (m, 1H), 3.33 (t, 4H), 3.60 (s, 3H), 7.52 (d, 1H), 7.72 (d, 1H), 8.24 (s, 1H).
MS (m/z) / M+1= 470
HPLC (uv purity, λ= 214 nm): 99.53%

Example I19.3: R1= cyclohexyl, R2= methyl, R3= 4-chloro-3-[(pyridin-4-ylmethyl)-sulfamoyl]-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide
To a mixture of I19 (0.258 mmol, 0.1 g), triethylamine (0.516 mmol, 0.072 ml) and acetic acid (0.516 mml, 0.03 ml) in 1,2-dichloroethane, 4-pyridine carboxaldehyde (0.387 mmol, 0.037 ml) was added. The mixture was cooled to 0°C and sodium triacetoxyborohydride (0.516 mmol, 0.135 g) was added. After 24h of stirring at RT the same quantities of borohydride and aldehyde were added and the reaction was stirred for 15h.
The mixture was then filtered and the filtrate was diluted with dichloromethane, washed with water, brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The residue was purified on silica gel eluting with dichloromethane containing from 0 to 7% of methanol. The solid product was then washed with ether to give the title product.
Yield= 40%
^{1}H-NMR (400MHz , DMSO) δ ppm:1.15-1.39 (m, 5H), 1.54-1.60 (m, 1H), 1.70-1.80 (m, 4H), 2.60-2.67 (m, 1H), 3.50 (s, 3H), 4.18 (s, 2H), 7.22 (d, 2H), 7.67 (dd, 1H), 7.76 (dd, 1H), 8.06 (d, 1H), 8.39 (d, 2H), 8.73-8.78 (b, 1H).
MS (m/z) / M+1= 478
HPLC (uv purity, λ= 214 nm): 99.99%

Example I19.4: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-(2-morpholin-4-yl-ethyl-sulfamoyl)-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-N-(2-morpholin-4-yl-ethyl)-

benzenesulfonamide

2-Chloro-*N*-(2-chloro-ethyl)-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide was prepared by the procedure described in example I19.3 using an appropriate aldehyde and I19. The residue was purified by silica gel chromatography eluting with a gradient cyclohexane containing from 0 to 20% of ethyl acetate followed by an isocratic elution with ethyl acetate/cyclohexane (4/6).
Yield= 84%

To a mixture of this intermediate (0.866 mmol, 0.390 g), in presence of sodium iodide in ethanol (10 ml), morpholine (8.66 mmol, 0.756 ml) was added. After 15 h at reflux, the mixture was evapored to dryness and the crude material was basified with a saturated solution of sodium bicarbonate. After extraction with ethyl acetate, the organic layer was washed with brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 50% of ethyl acetate.
Yield= 65%
^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.50 (m, 5H), 1.61-1.69 (m, 1H), 1.80-1.89 (b, 4H), 2.30-2.39 (m, 4H), 2.41-2.49 (m, 2H), 2.59-2.68 (m, 1H), 3.00-3.09 (m, 2H), 3.60-3.73 (m, 7H), 5.81-5.89 (b, 1H), 7.54 (d, 1H), 7.73 (d, 1H), 8.32 (s, 1H).
MS (m/z) / M+1= 500/501
HPLC (uv purity, λ= 214 nm): 97.76%

Example I19.5: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-ethylsulfamoyl-phenyl

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide

The title compound was prepared as described in example I19.3. In this particular case, a large excess of acetaldehyde (20 equivalents) and triacetoxy borohydride (4 equivalents) were used and added once.
Yield= 50%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.13 (t, 3H), 1.22-1.50 (m, 5H), 1.61-1.68 (m, 1H), 1.78-1.87 (b, 4H), 2.57-2.64 (m, 1H), 2.97-3.04 (q, 2H), 3.60 (s, 3H), 4.90 (t, 1H), 7.53 (d, 1H), 7.77 (d, 1H), 8.30 (s, 1H).
MS (m/z) / M+1= 415/416
HPLC (uv purity, λ= 214 nm): 99.36%

Example I19.6: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[ethyl-(2-morpholin-4-yl-ethyl)-sulfamoyl]-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

To a mixture of I19.4 (0.100 mmol, 0.05 g), N-tetrabutyl ammonium hydrogen sulfate (0.02 mmol, 0.008 g), a solution of 50% of sodium hydroxide (1.25 mmol, 0.1 ml) in toluene (2 ml), ethylbromide (1 mmol, 0.075 ml) was added. The mixture was heated to 90°C for 5h and then evaporated to dryness. The residue was solubilized in ethyl acetate and the organic layer was washed with brine, dried over $MgSO_4$, filtered and then distilled under vaccum. The crude material was purified on silica gel chromatography eluting with a mixture of ethylacetate/cyclohexane in a ratio 1/9 then 2/8 to give the expected product.
Yield= 60%
^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.13 (t, 3H), 1.22-1.45 (m, 5H), 1.61-1.68 (m, 1H), 1.78-1.84 (b, 4H), 2.38-2.43 (m, 4H), 2.50-2.53 (t, 2H), 2.57-2.64 (m, 1H), 3.40-3.50 (m, 4H), 3.60-3.65 (m, 7H), 7.50 (d, 1H), 7.70 (d, 1H), 8.30 (s, 1H).
MS (m/z) / M+1 = 528/529
HPLC (uv purity, λ= 214 nm): 98.57%

Example I19.7: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[isopropyl-(2-morpholin-4-yl-ethyl)-sulfamoyl]-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide

The title compound was prepared as described in example I19.6 with 13 equivalents f isopropylbromide. The residue was

purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethylacetate.
Yield= 74%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.50 (d, 6H), 1.22-1.47 (m, 5H), 1.61-1.68 (m, 1H), 1.78-1.83 (b, 4H), 2.44-2.50 (m, 4H), 2.57-2.63 (m, 3H), 2.47-2.51 (t, 2H), 3.60 (s, 3H), 3.68-3.70 (m, 4H), 3.98-4.04 (m, 1H), 7.50 (d, 1H), 7.70 (d, 1H), 8.30 (s, 1H).
MS (m/z) / M+1= 542/543
HPLC (uv purity, λ= 214 nm): 96.86%

Example I19.8: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-{ethyl-[2-(2-methoxy-ethoxy)-ethyl]-sulfamoyl}-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide

To a solution of I19.5 (0.241 mmol, 0.1 g) in EtOH (4 ml), potassium carbonate (0.289 mmol, 0.040 g) was addedd and then the reaction mixture was heated at reflux for 30 min before the addition of 1-bromo-2-(2-methoxyethoxy)ethane (0.289 mmol, 0.040 ml). After 3h at reflux, 2.4 equivalents of the bromo derivative were added and the mixture was kept at reflux for additional 15h. The mixture was then evaporated to dryness and the residue was diluted in water and extracted with dichloromethane. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and evaporated t dryness. The crude material was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 10 to 60% ethylacetate.
Yield= 64%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.11 (t, 3H), 1.20-1.47 (m, 5H), 1.61-1.68 (m, 1H), 1.79-1.89 (b, 4H), 2.59-2.68 (m, 1H), 3.36 (s, 3H), 3.43-3.50 (m, 4H), 3.54-3.58 (m, 4H), 3.61-3.65 (m, 5H), 7.50 (d, 1H), 7.70 (d, 1H), 8.28 (s, 1H).
MS (m/z) / M+1= 518/520
HPLC (uv purity, λ= 214 nm): 99.9%

Example I19.9: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(3-dimethylamino-2-hydroxy-propyl)-ethyl-sulfamoyl]-phenyl C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide

An excess of epibromohydrin (3 molar equivalents) was reacted with I19.5 following the procedure described in example I19.8. The intermediate was isolated by chromatography on silica gel eluting with a mixture of cyclohexane/ethylacetate in a ratio 1/9. To a solution of this intermediate (0.106 mmol, 0.05 g) in EtOH (2 ml) at 50°C, dimethylamine (0.318 mmol, 0.041 ml) was added and the mixture was heated at 70°C for 15h. The solvent was then removed under reduced pressure. The residue was diluted in water and extracted with dichloromethane. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and the volatile was evaporated to give the desired product.

Yield= 64%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.10 (t, 3H), 1.22-1.49 (m, 5H), 1.60-1.70 (m, 1H), 1.79-1.89 (b, 4H), 2.254-2.36 (m, 8H), 2.58-2.66 (m, 1H), 3.31-3.34 (dd, 1H), 3.42-3.60 (m, 6H), 3.79-3.87 (m, 1H), 7.50 (d, 1H), 7.70 (d, 1H), 8.30 (s, 1H).

MS (m/z) / M+1= 516/517

HPLC (uv purity, λ= 214 nm): 96.60%

Example I19.10: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(2,3-dihydroxy-propyl)-ethyl-sulfamoyl]-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide

The title compound was prepared as described in example I19.8 with 3 eq. of 3-bromo-1,2-propane-diol and the reaction mixture was heated at reflux for 12h. The desired product was obtained after purification of the crude material by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 3% methanol.

Yield= 38%

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^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.10 (t, 3H), 1.22-1.49 (m, 5H), 1.62-1.68 (m, 1H), 1.79-1.89 (m, 4H), 2.17-2.22 (m, 1H), 2.59-2.66 (m, 2H), 3.40-3.48 (m, 3H), 3.51-3.57 (dd, 1H), 3.61 (s, 3H), 3.89-3.94 (m, 1H), 7.53 (d, 1H), 7.73 (d, 1H), 8.30 (s, 1H).
MS (m/z) / M+1= 489/490
HPLC (uv purity, λ= 214 nm): 98.41%

Example I19.11: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[ethyl-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-sulfamoyl]-phenyl
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide
The title compound was prepared as described in example I19.9 using the same intermediate and pyrrolidine (3eq) as nucleophile. The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 2 to 3% of methanol.
Yield= 27%
^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.10 (t, 3H), 1.19-1.47 (m, 5H), 1.64-1.70 (m, 1H), 1.77-1.90 (m, 4H), 2.48-2.51 (dd, 1H), 2.53-2.78 (m, 7H), 3.33-3.37 (dd, 1H), 3.45-3.54 (m, 2H), 3.56 (d, 2H), 3.61 (s, 3H), 3.87-3.95 (m, 1H), 7.51 (d, 1H), 7.72 (d, 1H), 8.30 (s, 1H).
MS (m/z) / M+1= 542/543
HPLC (uv purity, λ= 214 nm): 95.50%

Example I19.12: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(2-diethylamino-ethyl)-ethyl-sulfamoyl]-phenyl
2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide
The title compound was prepared as described in example I19.8 using 3.3 eq of potassium carbonate and 2eq of 2-diethylaminoethylchl ride hydrochloride. The residue was purified by silica gel chromatography eluting with a mixture

of MeOH/DCM (10/90).
Yield= 32%
^{1}H-NMR (400MHz,CDCl3) δ ppm: 1.00 (t, 6H), 1.17 (t, 3H), 1.22-1.48 (m, 5H), 1.61-1.70 (b, 1H), 1.80-1.90 (m, 4H), 2.48-2.53 (q, 4H), 2.59-2.63 (m, 3H), 3.40-3.45 (m, 4H), 3.63 (s, 3H), 7.50 (d, 1H), 7.72 (d, 1H), 8.30 (s, 1H).
MS (m/z) / M+1= 514/ 515
HPLC (uv purity, λ= 214 nm): 99.34%

Example I19.13: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(2-dimethylamino-1-methyl-ethyl)-ethyl-sulfamoyl]-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-methyl-ethyl)-N-ethyl-benzenesulfonamide (minor isomer)
and Example I19.14: R1= cyclohexyl, R2= methyl, R3= 4-Chloro-3-[(2-dimethylamino-propyl)-ethyl-sulfamoyl]-phenyl 2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide (major isomer)
The title compounds were prepared by the procedure described in example I19.8 using 3.3 eq of potassium carbonate and 2eq of the of 2-dimethylaminoisopropylchloride hydrochloride.
Two "isomers" were obtained from this reaction:
The crude material was purified by silica gel chromatography eluting with dichloromethane/methanol (99/1) to afford two isomers.
The minor isomer:
Yield= 10%
^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.20-1.47 (m, 11H), 1.64-1.72 (m, 1H), 1.77-1.86 (m, 4H), 2.10 (s, 6H), 2.23-2.36 (m, 2H), 2.54-2.66 (m, 1H), 3.31-3.39 (m, 1H), 3.42-3.52 (m, 1H), 3.59 (s, 3H), 3.88-3.93 (m, 1H), 7.50 (d, 1H), 7.70 (d, H), 8.30 (s, 1H).
MS (m/z) / M+1= 500/ 501
HPLC (uv purity, λ= 214 nm): 98.67%

The major isomer:

Yield= 30%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 0.92 (d, 3H), 1.11 (t, 3H), 1.23-1.50 (m, 5H), 1.62-1.70 (m, 1H), 1.79-1.89 (m, 4H), 2.14 (s, 6H), 2.59-2.64 (m, 1H), 2.77-2.86 (m, 1H), 3.33-3.51 (m, 4H), 3.59 (s, 3H), 7.50 (d, 1H), 7.70 (d, H), 8.30 (s, 1H).

MS (m/z) / M+1= 500/ 501

HPLC (uv purity, λ= 214 nm): 99.67%

Example I20: R1= cyclohexyl, R2= methylacetate, R3= 4-chlorophenyl

[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester

To a solution of the appropriate 1,3,4-thiadiazole 7h (0.34 mmol, 100 mg) in anhydrous dioxane (3mL), an excess f methyl bromoacetate (3.4 mmol) was added. The resultant mixture was stirred for 48 h at 90°C. The mixture was concentrated and a saturated solution of K_2CO_3 was added. The solution was extracted with ethylacetate, the organic layer was dried over $MgSO_4$, filtered and concentrated t dryness. The residue was purified by chromatograpy on silica gel using a gradient of solvent cyclohexane/ethylacetat to afford 66 mg of product.

Yield= 52%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.35 (m, 5H), 1.55-1.60 (m, 1H), 1.65-1.75 (m, 4H), 2.65 (br, 1H), 3.65 (s, 3H), 4.77 (s, 2H), 7.53 (d, 2H), 7.67 (d, 2H).

MS (m/z) / M+1= 366/368

HPLC (uv putrity,λ= 214nm): 99.70%

The compounds of the following examples were prepared by the procedure described in example I20 using appropriate intermediates and reagents:

I20.1	[5-(4-Chloro-phenyl)-3-cyclopropylmethyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
I20.2	3-[5-(4-Chloro-phenyl)-2-cyclohexylimino-

	[1,3,4]thiadiazol-3-yl]-propane-1,2-diol
I20.3	[5-(4-Chloro-phenyl)-3-(2-diethylamino-ethyl)-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Example I21: R1= cyclohexyl, R2= methyl, R3= 3- benzoic acid methyl ester

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-benzoic acid methyl ester

To a solution of the appropriate 1,3,4-thiadiazole 7 (1.86 mmol, 590 mg) prepared by the procedure described in example 7g in anhydrous dioxane (20 mL), methyltrifluoromethane sulfonate (2.79 mmol, 316 µl) and triethylamine (2.23 mmol, 310 µl) were added. The mixture was stirred for 7h at RT. The mixture was filtered and the precipitate was then poured into diluted $NaHCO_3$ solution and washed with dichloromethane. The organic layer was washed with saturated solution of NaCl and dried over magnesium sulfate, filtered and concentrated under reduce pressure to give 200 mg of the title product.

Yield: 37%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.10-1.35 (m, 5H); 1.45-1.55 (m, 1H), 1.60-1.75 (m, 4H), 2.50-2.60 (m, 1H), 3.45 (s, 3H), 3.80 (s, 3H), 7.55 (t, 1H), 7.80 (d, 2H), 7.95 (d, 2H), 8.10 (s, 1H).

MS (m/z) / M+1= 332.3

HPLC (uv purity, λ= 214 nm): 99.9%

Example I21.1: R1= cyclohexyl, R2= methyl, R3= 3-benzoic acid

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid

To a solution of compound I21 (30 mg, 0.09 mmol) in methanol (10 ml) and water (2.5 ml), K_2CO_3 (163 mg,1.17 mmol) was added. The mixture was heated at reflux for 3h, allowed t cool and concentrated in vacuo to give a crude material. This residue was poured int water and the suspension was carefully neutralised with a s lution of HCl (0.1N) and the

aqueous phase was extracted with ethyl acetate. The organic layer was washed with saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give 10 mg f the title product.

Yield: 35%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 7.55 (t, 1H), 7.80 (d, 1H), 7.95 (d, 1H), 8.15 (s, 1H), 13.3 (bs, 1H).

MS (m/z) / M+1= 318.3

HPLC (uv purity, λ= 214 nm): 99.6%

Example I21.2: R1= cyclohexyl, R2= methyl, R3= 3-benzamide

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

To a solution of LiOH monohydrate (96 mg, 2.26 mmol) in 1.6 ml of water, a solution of I21 (500 mg, 1.51 mmol) in tetrahydrofuran (THF)/MeOH (50/50) (8 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 38 ml) was added. The resulting mixture was stirred for 2 hours. After distillation of water ,the product was dried over P_2O_5 in vacuo. To a solution of this crude material (1.51 mmol) in toluene (10 ml), thionylchloride (10 ml) was added dropwise and the mixture was heated at reflux for 5H. The mixture was concentrated under reduced pressure. A solution of ammonia (1 ml at 28%) was added to a solution of the residue (150 mg, 0.32 mmol) in THF (2 ml) cooled to 10°C. After 3 hours at RT, the mixture was concentrated to dryness, poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water and with a saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled under reduced pressure. The white solid material was purified by silica gel chromatography (eluted with dichloromethane/methanol at 99/1) to afford 14mg f the title product.

Yield: 14%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.60-1.70 (m, 1H), 1.75-1.90 (m, 4H), 2.65-2.75 (m, 1H), 3.60 (s, 3H), 7.52(s, 1H), 7.60 (dd, 1H), 7.85 (d, 1H), 7.98 (d, 1H), 8.15(s, 1H), 8.18(s, 1H).

MS (m/z) / M+1= 317

HPLC (uv purity, λ= 214 nm): 99.9%

Example I21.3: R1= cyclohexyl, R2= methyl, R3= 3-[N-(2-hydroxy-ethyl)]-benzamide

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide

To a solution of LiOH monohydrate (96 mg, 2.26 mmol) in 1.6 ml of water, a solution of I21 (500 mg, 1.51 mmol) in THF/MeOH (50/50) (8 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 38 ml) was added. The resulting mixture was stirred for 2 hours. After distillation of water ,the product was dried over P_2O_5 in vacuo. To a solution of this crude material (1.51 mmol) in toluene (10 ml), thionylchloride (10 ml) was added dropwise and the mixture was heated at reflux for 5H. The mixture was concentrated under reduced pressure. To a suspension of this residue (150 mg, 0.32 mmol) in THF (2ml) with triethylamine (90 µl, 0.64 mmol) was added at 0°C ethanolamine (20 µl, 0.32 mmol) and stirred at room temperature during 4 hours. Water was added in the mixture and extracted with ethyl acetate, washed with water and brine, dried with magnesium sulfate, filtred and reduce under pressure vacuum. The residue was purified by silica gel chromatography with a gradient of dichlorometane containig from 0 to 2% methanol to afford 50 mg of the good product.

Yield: 43%

1H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.83 (m, 4H), 2.55-2.75 (m, 1H), 3.30-3.37 (m, 2H), 3.45-3.55 (m, 5H), 4.70 (t, 1H), 7.55(dd, 1H), 7.80 (d, 1H), 7.90 (d, 1H), 8.05(s, 1H), 8.60(t, 1H).

MS (m/z) / M+1= 361

HPLC (uv purity, λ= 214 nm): 99.7%

Example I21.4: R1= cyclohexyl, R2= methyl, R3= 3-(N-methyl)-benzamide

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiasol-2-yl)-N-methyl-benzamide

To a solution of LiOH monohydrate (96 mg, 2.26 mmol) in 1.6 ml of water, a solution of I21 (500 mg, 1.51 mmol) in THF/MeOH (50/50) (8 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 38 ml) was added. The resulting mixture was stirred for 2 hours. After distillation of water ,the product was dried over P_2O_5 in vacuo. To a solution of this crude material (1.51 mmol) in toluene (10 ml), thionylchloride (10 ml) was added dropwise and the mixture was heated at reflux for 5H. The mixture was concentrated under reduced pressure. To a suspension of this residue (150 mg, 0.32 mmol) in THF (4 ml) with triethylamine (90 µl, 0.64 mmol) was added at 0°C methylamine hydrochloride (44 mg, 0.64 mmol) and stirred at room temperature during 4 hours. Water was added in the mixture and basified with a solution of $NaHCO_3$, extracted with ethyl acetate; washed with water and brine, dried with magnesium sulfate, filtred and reduce under pressure vacuum. The residue was purified by silica gel chromatography with a gradient of dichlorometane containig from 0 to 2% methanol to afford the desired product.

Yield: 9%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 2.82 (s, 3H), 3.55 (s, 3H), 7.60(t, 1H), 7.80 (d, 1H), 7.90 (d, 1H), 8.05(s, 1H), 8.55-8.65 (m, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ= 214 nm): 96.6%

Example I22: R1= cyclohexyl, R2= methyl, R3= 3,4-dihydroxyphenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiaz 1-2-yl)-benzene-1,2-diol; compound with trifluoro methanesulfonic acid

Compound I22 was prepared from 1,3,4-thiadiazole 7g by the procedure described in example I18 using appropriate intermediates and reagents (protocol C).
In this particular case, the mixture was filtered and the precipitate was washed with dioxane and diethylether to give the expected compound as a trifluoromethanesulfonic acid salt.
Yield= 54.1%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.53 (m, 5H), 1.64-1.69 (b, 1H), 1.78-1.84 (b, 1H), 2.03-2.10 (b, 2H), 3.19-3.27 (b, 1H), 3.84 (s, 3H), 6.90 (d, 1H), 7.13 (d, 1H), 7.20 (s, 1H), 9.55-9.63 (b, 1H), 9.75-9.81 (b, 1H), 9.96-10.3(b, 1H).
MS (m/z) / M+1= 306/307
HPLC (uv purity, λ= 214 nm)= 97.35 %

Example I23: R1= cyclohexyl, R2= methyl, R3= 3,5-dimethoxy-4-hydroxy-phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-2,6-dimethoxy-phenol

Compound I23 was prepared from the appropriate 1,3,4-thiadiazole 7 by the procedure described in example I18 using appropriate intermediates and reagents (protocol C).
In this particular case, the mixture was filtered and the precipitate was washed with dioxane and diethylether to give the expected compound as a trifluoromethansulfonic acid salt.
Yield= 13.9%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.12-1.27 (b, 1H), 1.27-1.41 (b, 2H), 1.41-1.54 (b, 2H), 1.63-1.70 (b, 1H), 1.80-1.87 (b, 2H), 2.03-2.11 (b, 2H), 3.17-3.26 (b, 1H), 3.88 (9H, s), 7.06 (s, 2H), 9.38-9.47 (b, 1H), 9.80-9.88 (b, 1H).
MS (m/z) / M+1= 350/351

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HPLC (uv purity, λ= 214 nm)= 96.00%

Compounds I23.1 and I23.2 were prepared by the procedure described in example I18 using appropriate intermediates and reagents (protocol C).

I23.1	6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol
I23.2	5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol

Example I24: R1= cyclohexyl, R2= methyl, R3= 8-hydroxyquinolin-2-yl

2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-quinolin-8-ol

Compound I24 was prepared from the appropriate 1,3,4-thiadiazole 7 (procedure described in example 7d) by the procedure described in example I18.6. In this particular case, the mixture was filtered and the precipitate was washed with dioxane and diethylether to give the expected compound as a trifluoromethansulfonic acid salt.

Yield =58.1%

^{1}H-NMR (400MHz, DMSO) δ ppm:1.25-1.36 (b, 1H), 1.45-1.67 (b, 4H), 1.74-1.81 (b, 1H), 1.90-1.96 (b, 2H), 2.18-2.22 (b, 2H), 3.40-3.50 (b, 1H), 4.02 (s, 3H), 7.35 (d, 1H), 7.63 (d, 1H), 7.69 (t, 1H), 8.21 (d, 1H), 8.64 (d, 1H), 10.08-10.13 (b, 1H), 10.21-10.28 (b, 1H).

MS (m/z) / M+1= 341/342

HPLC (uv purity, λ= 214 nm)= 94.88%

Example I25: R1= cyclohexyl, R2= methyl, R3= 2-pyrasyl

Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4] thiadiazol-2-ylidene)-amine

The 1,3,4-thiadiazole 7f (0.770 mmol, 0.200 g) and methyltrifluoromethane sulfonate (0.924 mmol, 0.104 ml) were reacted in dioxane (7 ml). The residue, obtained after basification t pH 9-10 with a saturated solution of

carbonate of potassium, was subjected to silica gel chromatography, eluting with dichloromethane containing from 0 to 10% methanol to give the expected product.

Yield= 0.075g, 35.37%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.43 (b, 5H), 1.56-1.65 (b, 1H), 1.90-2.00 (b, 4H), 2.63-2.70 (b, 1H), 3.56 (s, 3H), 8.67 (s, 2H), 9.12 (s, 1H).

HPLC (uv purity, λ= 214 nm)= 98.32%

MS (m/z) / M+1= 276/277

Example I26: R1 =cyclohexyl, R2= methyl, R3= (E)-2-(3-hydroxy-4-methoxy-phenyl)-vinyl

5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol

Compounds I26 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7d) and reagents.The desired product was isolated by chromatography on silica gel eluting with dichloromethane containing from 0 to 7% methanol.

Yield= 0.025g, 24.1%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.36 (b, 6H), 1.52-1.59 (b, 1H), 1.66-1.78 (b, 4H), 3.39 (s, 3H), 3.76 (s, 3H), 6.70-6.80 (b, 1H), 6.85-6.97 (b, 2H), 6.97-7.07 (b, 2H), 9.04 (s, 1H).

MS (m/z) / M+1= 346/347

HPLC (uv purity, λ= 214 nm)= 98.64%

Example I27: R1= cyclohexyl, R2= methyl, R3= 3-methoxy-4-hydroxy-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol

Compounds I27 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7d) and reagents.The desired product was is lated by chromatography on silica gel (Alltech, 2g silice) eluting with cyclohexane

containing from 0 to 4% ethylacetate.
Yield= 0.015 g, 14.2%
^{1}H-NMR (400MHz, DMSO) δ ppm:1.01-1.20 (b, 5H), 1.39-1.44 (b, 1H), 1.53-1.63 (b, 4H), 2.4-2.48 (b, 1H), 3.30 (s, 3H), 3.65 (s, 3H), 6.64 (d, 1H), 6.87 (d, 1H), 7.00 (d, 1H), 9.38-9.43 (b, 1H).
MS (m/z) / M+1= 320/321
HPLC (uv purity, λ= 214 nm)= 99.08%

Example I28: R1= cyclohexyl, R2= methyl, R3= quinolin-8-yl
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine
Compounds I28 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 20% AcOEt.
Yield: 41%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.70-2.80 (m, 1H),3.45 (s, 3H), 7.55-7.60 (m, 1H), 7.60-7.70 (m, 1H), 7.95-8.05 (m, 1H), 8.35-8.40 (m, 1H), 8.40-8.45 (m, 1H), 8.20-8.80 (m, 1H).
MS (m/z) / M+1= 325.3
HPLC (uv purity, λ= 214 nm): 99.9%

Example I29: R1= cyclohexyl, R2= methyl, R3= 4-dimethylamino-phenyl
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine
Compounds I29 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.The product was chromatographed on silica gel column using cyclohexane/ethyl acetate with a ratio 8/2 as solvent.
Yield: 27%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.80 (m, 4H), 2.50-2.60 (m, 1H), 3.45 (s, 3H), 6.70 (d, 2H), 7.40 (d, 2H).

MS (m/z) / M+1= 317.3

HPLC (uv purity, λ= 214 nm): 99.5%

Example I30: R1= cyclohexyl, R2= methyl, R3= 4-sulfonamide-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-benzenesulfonamide

Compounds I30 was prepared by the procedure described in example I18 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

The residue was subjected to silica gel chromatography, eluting with cyclohexane containing from 0 to 20% AcOEt.

Yield: 21%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 4H), 2.50-2.60 (m, 1H), 3.45 (s, 3H), 7.40 (s, 2H), 7.75 (d, 2H), 7.85 (d, 2H).

MS (m/z) / M+1= 353.2

HPLC (uv purity, λ= 214 nm): 98.5%

Example I31: R1= cyclohexyl, R2= methyl, R3= 5-chloroindol-2-yl

[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid

Compounds I31 was prepared by the procedure described in example I18.6 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

In this particular case, the mixture was filtered and the precipitate was washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.

Yield: 88%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.55 (m, 5H), 1.60-1.70

(m, 1H), 1.75-1.85 (m, 2H),1.95-2.10 (m, 2H), 3.10-3.30 (m, 1H), 3.85 (bs, 3H), 7.10-7.15 (m, 1H), 7.15-7.20 (m, 1H), 7.40-7.50 (m, 1H), 7.75 (bs, 1H), 10 (bs, 1H), 12.40 (bs, 1H).

MS (m/z) / M+1= 347.3

HPLC (uv purity, λ= 214 nm): 95.2%

Compound I31.1 was prepared by the procedure described in example I31 using appropriate intermediates and reagents:

I31.1	2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

Example I32: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-4-methoxy-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

Compounds I32 was prepared by the procedure described in example I18.6 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

In this particular case, the mixture was concentrated, filtered and the precipitate was washed with ethyl acetate to give the expected compound as a salt f trifluoromethansulfonic acid.

Yield: 69%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.05-1.45 (m, 5H), 1.50-1.60 (m, 1H), 1.70-1.80 (m, 2H),1.90-2.05 (m, 2H), 3.05-3.20 (m, 1H), 3.8 (2s, 6H), 7.00 (d, 1H), 7.15-7.20 (m, 2H), 9.60 (bs, 1H), 9.75 (bs, 1H).

MS (m/z) / M+1= 320.3

HPLC (uv purity, λ= 214 nm): 98%

Example I33: R1= cyclohexyl, R2= methyl, R3= 4-hydroxy-phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid

Compounds I33 was prepared by the procedure described in example I18.6 using appropriate intermediate (1,3,4-thiadiazole 7 - procedure described in example 7b) and reagents.

In this particular case, the mixture was filtered and the precipitate was washed with ethyl acetate to give the expected compound as a salt of trifluoromethansulfonic acid.

Yield: 95%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.05-1.45 (m, 5H), 1.50-1.60 (m, 1H), 1.65 -1.75 (m, 2H),1.90-2.00 (m, 2H), 3.30-3.40 (m, 1H), 3.75 (s, 3H), 6.85 (d, 2H), 7.60 (d, 2H), 9.70 (bd, 1H), 10.25 (bd, 1H).

MS (m/z) / M+1= 290.3

HPLC (uv purity, λ= 214 nm): 95.6%

Example I34: R1= cyclohexyl, R2= methyl, R3= 3,4-dimethoxy-phenyl
Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I34 was prepared from the appropriate 1,3,4-thiadiazole 7 by the procedure described in example I17 (protocol C) using appropriate intermediates and reagents.

The desired product was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 20% ethylacetate.

Yield: 28%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.30 (m, 5H), 1.45-1.55 (m, 1H), 1.60-1.75 (m, 4H), 2.45-2.60 (m, 1H), 3.40 (s, 3H), 3.70 (2s, 6H), 6.95 (d, 1H), 7.05 (d, 1H), 7.10 (s, 1H)

MS (m/z) / M+1= 334.3

HPLC (uv purity, λ= 214 nm): 98.2%

Example I35: R1= cyclohexyl, R2= methyl, R3= 3-bromo-4-

methoxy-phenyl

[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

Compound I35 was prepared from 1,3,4-thiadiazole 7e, by the procedure described in example I17 (protocol C) using appropriate intermediates and reagents.

The desired product was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 15% ethylacetate.

Yield: 13%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 3.90 (s, 3H), 7.20 (d, 1H), 7.60 (d, 1H), 7.85 (s, 1H)

MS (m/z) / M+1= 384.2

HPLC (uv purity, λ= 214 nm): 95%

The compounds of the following examples were prepared by the procedure described in example I35 using appropriate intermediates and reagents:

I35.1	Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine
I35.2	Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Example I36: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-phenyl

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadias 1-2-yl)-phenol

Compound I36 was prepared from the appropriate 1,3,4-thiadiazole 7 by the procedure described in example I17 (protocol C), using appropriate intermediates and reagents.

The product was chromatographed on silica gel column using a gradient of cyclohexane/ethyl acetate.

Yield: 14%

^{1}H-NMR (400MHz , DMSO) δ ppm : 1.15-1.40 (m,5H), 1.55-1.65 (m,1H), 1.70-1.85 (m,4H), 2.55-2.65 (m,1H), 3.50 (s,3H), 6.85 (d,1H), 7.00-7.05 (m,2H), 7.25 (t,1H), 9.75 (s,1H)

MS (m/z) / M+1 =290.29

HPLC (uv purity, λ= 214 nm): 93.9%

Example I37: R1= cyclohexyl, R2= methyl, R3= 4-benzoic acid methyl ester

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-benzoic acid methyl ester

Compound I37 was prepared from the approriate 1,3,4-thiadiazole 7 by the procedure described in example I17 (protocol C) using appropriate intermediates and reagents. The product was chromatographed on silica gel column using a gradient of cyclohexane/ethyl acetate.

Yield: 47%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.65-1.75 (m, 4H), 2.50-2.65 (m, 1H), 3.50 (s, 3H), 3.80 (s, 3H), 7.70 (d, 2H), 8.00 (d, 2H).

MS (m/z) / M+1= 332.3

HPLC (uv purity, λ= 214 nm): 99.9%

Example I37.1: R1= cyclohexyl, R2= methyl, R3= 4-benzoic acid

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-benzoic acid

To a solution of 1,3,4-thiadiazol I37 (80 mg,0.24 mmol) in methanol (10 ml) and water (2.5 ml), K_2CO_3 (434 mg,3.14 mmol) was added. The mixture was heated at 65°C during 3h then at RT over night. The solvent was removed by distillation under reduced pressure to give a crude material. This residue was poured into water, the suspension was carefully neutralised with a solution of HCl (0.1N) and the aqueous phase was extracted with dichloromethane. The organic layer was washed with saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give 40 mg of the title product.

Yield: 52%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.55 (s, 3H),

7.75 (d, 2H), 8.00 (d, 2H), 13.15 (bs, 1H).
MS (m/z) / M+1= 318.4
HPLC (uv purity, λ= 214 nm): 99.9%

Example I37.2: R1= cyclohexyl, R2= methyl, R3= 4-hydroxamic acid phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide

To a solution of LiOH monohydrate (37 mg, 0.75 mmol) in 0.8 ml of water; a solution of compound I37 (250 mg, 0.75 mmol) in THF/MeOH (50/50) (4 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water (2 ml) and a solution of HCl (0.1N, 15 ml) was added. The resulting mixture was stirred for 20 min. After distillation of water, the crude product was dried over P_2O_5 in vacuo. To a solution of 75 mg (0.19 mmol) of this crude material in toluene (1 ml), a drop of pyridine, and thionylchloride (70 µl) were added and reacted at reflux during 4H. The volatiles were removed under reduced pressure. To a solution of this residue in anhydrous THF, O-(trimethylsilyl) hydroxylamine (230 µl, 0.47 mmol) was added with molecular sieves (3A) and the reaction mixture was stirred for 18H at RT. After filtration, the filtrate was concentrated under reduced pressure and the residue was treated with a 1 M solution of HCl, stirred at RT and then basified with a solution of $NaHCO_3$. The aqueous phase was extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The title product was isolated by preparative HPLC on inverse phase (HYPERSYL C18) eluting with water containing from 5 to 95% acetonitrile during 20 mn.
Yield: 12 mg, 20%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.50 (s, 3H), 7.65 (d, 2H), 7.85 (d, 2H);
MS (m/z) / M+1= 333.2

HPLC (uv purity, λ= 214 nm): 94.9%

Example I37.3: R1= cyclohexyl, R2= methyl, R3= 4-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

To a solution of LiOH monohydrate (126 mg, 3.0 mmol) in 0.8 ml of water, a solution of I37 (1.0g, 3mmol) in THF/MeOH (50/50) (4 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water (8 ml) and a solution of HCl (0.1N, 60 ml) was added. The resulting mixture was stirred for 20 min. After distillation of water ,the product was dried over P_2O_5 in vacuo. To a solution of 120 mg (0.3 mmol) of this crude material in 2 ml of toluene, thionylchloride (2 ml) was added dropwise and the mixture was heated at reflux for 4H. The mixture was concentrated under reduced pressure. A solution of ammonia (1 ml at 28%) was added to a solution of the residue in THF (2 ml) cooled to 10°C. After allowing to stand 5 hours at RT, the mixture was concentrated to dryness, poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water and with a saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled under reduced pressure. The white solid material was purified by silica gel chromatography (eluted with dichloromethane) t afford 64mg of the title product.

Yield: 67%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.45(bs, 1H), 7.75 (d, 2H), 7.95 (d, 2H), 8.05 (bs, 1H).

MS (m/z) / M+1= 317.35

HPLC (uv purity, λ= 214 nm): 99.3%

Example I37.4: R1= cyclohexyl, R2= methyl, R3= 4-N-(2H-tetrazol-5-yl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2H-tetrazol-5-yl)-benzamide hydrochloride salt

To a solution of LiOH monohydrate (187 mg, 4.5 mmol) in 0.8 ml of water ,a solution of compound I37 (250 mg, 0.75 mmol) in THF/MeOH (50/50) (4 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water (2 ml) and a 0.1 M solution of HCl was added to reach pH 6-7. After distillation of water, the crude material was dried over P_2O_5 in vacuo. Morpholine type resin (180 mg, 0.62 mmol) was added to a solution of 450 mg (0.62 mmol) of this crude material in 15ml of THF cooled to -15°C. Then isobutylchloroformate (105 µl; 0.8mmol) was added and the mixture was stirred at -15°C for 1H30 before addition f a suspension of amino-1H-tetrazole (80 mg, 0.74 mmol) in THF (10 ml). The reaction mixture was allowed to stand overnight at RT and the mixture was filtered over a silica gel. The filtrate was concentrated to dryness, and purified by preparative HPLC on inverse phase C18 (HYPERSYL), eluting with water containing from 5 to 95% acetonitrile in 20 min to afford 10 mg of the title product. The compound was treated with a solution of ethanol/HCl to give the corresponding hydrochloride salt.

Yield: 4%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-2.15 (m, 10H), 3.10-3.30 (m, 1H), 4.00 (bs, 3H), 8.10 (bd, 2H), 8.35 (bd, 2H), 12.70 (bs, 1H).

MS (m/z) / M+1= 385.46

HPLC (uv purity, λ= 214 nm): 99.9%

Example I37.5: R1= cyclohexyl, R2= methyl, R3= 4-(N-quinolin-8-yl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide

To a solution of LiOH monohydrate (794 mg, 19mmol) in 18 ml of water, a solution of I37 (5.7 g, 17.2mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT

for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred f r 3H30. After distillation of water, the crude product was dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5 mmol) of this crude material in CH_2Cl_2/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), 1-hydroxy-7-azabenzotriazol (14 mg, 0.1mmol), N,Ndiisopropylethylamine (175 µl, 1 mmol), 8-aminoquinoline (145 mg, 1 mmol), molecular sieves (3A) and the reaction mixture was stirred 24H at RT. After filtration, methylisocyanate resin (1 g, 1 mmol) was added to the filtrate and the mixture was stirred for another 24H at RT. The mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethyl acetate to afford 10 mg f the title product.

Yield: 4.5%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.60-1.65 (m, 1H), 1.75-1.85 (m, 4H), 2.65-2.75 (m, 1H), 3.55 (s, 3H), 7.65-7.75 (m, 2H), 7.80 (d, 1H), 7.90 (d, 2H), 8.15 (d, 2H), 8.5 (d, 1H), 8.75 (d, 1H), 9.00 (d, 1H), 10.70 (s, 1H).

MS (m/z) / M+1= 444.13

HPLC (uv purity, λ= 214 nm): 96.4%

Example I37.6: R1= cyclohexyl, R2= methyl, R3= 4-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiaz l-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide

To a solution of LiOH monohydrate (794 mg, 19 mmol) in 18 ml of water, a solution of I37 (5.7 g, 17.2 mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred f r 3H30. After distillation f water, the crude product was

dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5 mmol) of this crude material in CH_2Cl_2/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), 1-hydroxy-7-azabenzotriazol (14 mg, 0.1 mmol), N,Ndiisopropylethylamine (260 µl, 1.5 mmol), 3-amino-2,6-dimethoxypyridine monohydrochloride (190 mg, 1mmol), molecular sieves (3A) and the reaction mixture was stirred 24h at RT. After filtration, methylisocyanate resin (1 g, 1 mmol) was added to the filtrate and the mixture was stirred for another 24H at RT. The mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 10% ethyl acetate to afford 60 mg of the title product.

Yield: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.35 (m, 5H), 1.50-1.60 (m, 1H), 1.70-1.80 (m, 4H), 2.55-2.65 (m, 1H), 3.50 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 6.35 (d, 1H), 7.70-7.80 (m, 3H), 8.00 (d, 2H), 9.65 (s, 1H).

MS (m/z) / M+1= 454

HPLC (uv purity, λ= 214 nm): 99.9%

Example I37.7: R1= cyclohexyl, R2= methyl, R3= 4-N-isopropyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide

To a solution of LiOH monohydrate (794 mg, 19 mmol) in 18 ml of water , a solution of I37 (5.7g, 17.2 mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred f r 3H30. After distillation of water, the crude product was dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5 mmol) of this crude material in CH_2Cl_2/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), 1-hydroxy-7-azabenz triaz l (15 mg, 0.1mmol),

N,Ndiisopropylethylamine (175 µl, 1 mmol), isopropylamine (85 µl, 1 mmol), molecular sieves (3A) and the reaction mixture was stirred 24H at RT. After filtration, Methylisocyanate resin (1 g, 1 mmol) was added to the filtrate and the mixture was stirred for another 24H at RT. The mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 20% ethyl acetate to afford 40 mg f the title product.

Yield: 22%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 11H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 4.05-4.15 (m, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.30 (d, 1H).

MS (m/z) / M+1= 359

HPLC (uv purity, λ= 214 nm): 99.9%

Example I37.8: R1= cyclohexyl, R2= methyl, R3= 4-N-ethyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiaz 1-2-yl)-N-ethyl-benzamide

To a solution of 2M ethylamine (1.8 ml, 3.6 mmol) in dichloroethane (5 ml) under nitrogen at 0°C, was added 2M trimethylaluminium (1.8 ml, 3.6 mmol) and the mixture was stirred at RT for 15min. Then, a solution of compound I37 (180 mg, 0.54 mmol) in dichloroethane (5 ml) was added and the reaction mixture was allowed to stir for 48 h at RT. A solution of 2M ethylamine (0.8 ml, 1.6 mmol) and of 2M trimethylaluminium (0.8 ml, 1.6 mmol) were added to allow reaction to completion and the mixture was stirred at RT for another 24H. The mixture was diluted with 50 ml of dichloromethane and 30 ml of water, stirred for 2H, and filtered through Celite. The filtrate was washed with water, brine and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected t flash chromatography eluting with a gradient f cycl hexane containing from 0 to 20% ethyl acetate t aff rd

60 mg of the title product.
Yield: 32%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20 (t, 3H), 1.20-1.50 (m, 5H), 1.60-1.70 (m, 1H), 1.80-1.95 (m, 4H), 2.70-2.80 (m, 1H), 3.35-3.45 (m, 2H), 3.65 (s, 3H), 7.90 (d, 2H), 8.05 (d, 2H), 8.65 (m, 1H).
MS (m/z) / M+1= 344.7
HPLC (uv purity, λ = 214 nm): 99.9%

Example I37.8-1: R1= cyclohexyl, R2= methyl, R3= 4-(1-ethyl-1H-tetrazol-5-yl)-phenyl
Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine
To a solution of I37.8 (0.29 mmol, 100 mg) in acetonitrile (3 ml) at 0°C under a nitrogen atmosphere, sodium azide (0.44mmol, 28mg) and trifluoromethanesulfonic anhydre (0.44 mmol, 73 µl) were added. Then, the mixture was stirred overnight at room temperature and a satured solution of $NaHCO_3$ to pH=7 was added. The aqueous layer was extracted with dichloromethane and the organic layer was washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with a gradient of dicloromethane/methanol, then by HPLC (C_{18}-HYPERSYL column), eluting with water containing from 5 to 95% acetonitrile in 20 min to afford the title product.
Yield: 9%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.47 (t, 3H), 1.55-1.65 (m, 1H), 1.70-1.82 (m, 4H), 2.50-2.55 (m, 1H), 3.55 (s, 3H), 4.52 (q, 2H), 7.85-7.90 (m, 4H).
MS (m/z) / M+1= 370
HPLC (uv purity, λ = 214 nm)= 96.8%

Example I37.9: R1= cyclohexyl, R2= methyl, R3= 4-N-(2-dimethylamino-ethyl)-benzamide
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide

To a solution of N,N-dimethylethylenediamine (335 µl, 3 mmol) in dichloroethane (5 ml) under nitrogen atmosphere at 0°C, was added 2M trimethylaluminium (1.5 ml, 3 mmol), and the mixture was stirred at RT for 1H30. Then, a solution of compound I37 (180 mg, 0.54 mmol) in dichloroethane (5 ml) was added and the reaction mixture was allowed to stir for 24 h at RT and 24h at 45°C. The mixture was diluted with 10ml of dichloromethane and 20ml of water, stirred for 1H30, and filtered through Celite. The filtrate was washed with water, brine and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with a gradient of dichloromethane containing 0 t 5% methanol to afford 140 mg of the title product.

Yield: 60%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.25 (s, 6H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 7.75 (d, 2H), 7.90 (d, 2H), 8.50 (m, 1H)

MS (m/z) / M+1= 388

HPLC (uv purity, λ = 214 nm): 99.4%

Example I37.10: R1= cyclohexyl, R2= methyl, R3= 4-N-pyridin-4-ylmethyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide

To a solution of LiOH monohydrate (794 mg, 19 mmol) in 18 ml of water , a solution of compound I37 (5.7 g, 17.2 mmol) in THF/MeOH (50/50) (100 ml) was added. The mixture was stirred at RT for 24H and then concentrated under reduced pressure. The residue was dissolved in water and a solution of HCl (0.1N, 361 ml) was added. The resulting mixture was stirred for 3H30. After distillation of water, the crude product was dried over P_2O_5 in vacuo. To a suspension of 200 mg (0.5 mmol) of the crude material in CH_2Cl_2/DMF (50/50) (6 ml) were added cyclocarbodiimide-N-methyl resin (1.03 g, 1.5 mmol), O-(7-azabenz triaz l-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluorophosphate (38 mg, 0.1mmol),

N,Ndiisopropylethylamine (175 µl, 1 mmol), 4-picolylamine (105 µl, 1 mmol), molecular sieves (3A) and the reaction mixture was stirred 3 days at RT. This mixture was filtered, and in the organic layer was added methylisocyanate resin (1 g, 1 mmol) and stirred 3 days at RT. After filtration, the filtrate was concentrated under reduced pressure. The s lid was poured into water and the mixture was stirred for 1 h, before extraction with dichloromethane. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 5% methanol to afford 30 mg of the title product.

Yield: 15%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.75 (m, 1H), 3.55 (s, 3H), 4.50 (d, 2H), 7.35 (d, 2H), 7.75 (d, 2H), 8.00 (d, 2H), 8.50 (d, 2H), 9.25 (m, 1H).

MS (m/z) / M+1= 408

HPLC (uv purity, λ = 214 nm): 99.7%

Example I37.11: R1= cyclohexyl, R2= methyl, R3= 4-N-methyl-N-(1-methyl-piperidin-4-yl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-N-(1-methyl-piperidin-4-yl)-benzamide

To a solution of I37.1 (0.5 mmol, 200 mg) in DMF (2.5 ml), ethyl-diisopropyl-amine (1.6 mmol, 190 µl), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.6 mmol, 265 mg), 1-hydroxy-7-azabenzotriazole (0.25 mmol, 34 mg) and 1-methyl-4-(methylamino)piperidine (0.6 mmol, 87 µl) were added and the reaction mixture was stirred at room temperature overnight. The solvent was distilled under reduced pressure and the residue was poured into water before extraction with dichloromethane. The organic layer was washed with brine and then with a saturated s lution of $NaHCO_3$, dried over magnesium sulfate, filtered and concentrated under vaccum. The residue was purified by

silica gel chromatography using a gradient f dichloromethane containing 0 to 15% methanol, to give the desired product.

Yield: 93.5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.23-1.45 (m, 5H), 1.55-1.65 (m, 1H), 1.68-1.85 (m, 6H), 1.85-2.00 (m, 2H), 2.23-2.44 (m, 5H), 2.55-2.65 (m, 1H), 2.83 (s, 3H), 3.00-3.10 (m, 2H), 3.55 (s, 3H), 3.85-4.03 (m, 1H), 7.48 (dd, 2H), 7.70 (dd, 2H).

MS (m/z) / M+1= 428

HPLC (uv purity, λ = 214 nm)= 99.4%

Example I37.12: R1= cyclohexyl, R2= methyl, R3= 4-N-isobutyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-N-isobutyl-benzamide

To a solution of I37.1 (0.5 mmol, 200 mg) in DMF (2.5 ml), ethyl-diisopropyl-amine (1.6 mmol, 190 µl), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.6 mmol, 265 mg), 1-hydroxy-7-azabenzotriazole (0.25 mmol, 34 mg) and isobutylamine (2.3 mmol, 80 µl) were added and the reaction mixture was stirred at room temperature overnight. The solvent was distilled and the residue was poured int water before extraction with dichloromethane. The organic layer was washed with brine, a saturated solution of $NaHCO_3$, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the desired product.

Yield: 86%

^{1}H-NMR (400MHz , DMSO) δ ppm: 0.90 (d, 6H), 1.20-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.72-1.90 (m, 5H), 2.60-2.70 (m, 1H), 3.10 (t, 2H), 3.55 (s, 3H), 7.72 (dd, 2H), 7.92 (dd, 2H), 8.55 (t, 1H).

MS (m/z) / M+1= 373

HPLC (uv purity, λ = 214 nm)= 98.4%

Example I37.13: R1= cyclohexyl, R2= methyl, R3: 4-N-methyl-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide

To a solution of I37.1 (4.25 mmol, 1,7 g) in DMF (20,5 ml) was added N-ethyldiisopropylamine-N,N-diisopropylethylamine (13.6 mmol, 1.615 ml), benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate (5.1 mmol, 2.265 g), 1-hydroxy-7-azabenzotriazole (2.125 mmol, 290 mg) and a solution of methylamine at [2N] in methanol (5.1 mmol, 3.55 ml). The mixture was stirred at room temperature overnight. The mixture was reduced under pressure vacuum, extracted with dichloromethane in water. The organic layer was washed with brine, dried over magnesium sulfate and reduced under pressure vacuum. The residue was purified by silica gel chromatography using a gradient f dichloromethane containing 0 to 4% methanol, to give a residue which was stirred in diethylether during one hour. The precipitate was filtred and dried under vacuum over P_2O_5 to give 550 mg of the desired product.

Yield: 44%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.18-1.45 (m, 5H), 1.55-1.68 (m, 1H), 1.68-1.83 (m, 4H), 2.60-2.70 (m, 1H), 2.80 (d, 3H), 3.55 (s, 3H), 7.82 (dd, 2H), 7.92 (dd, 2H), 8.55 (q, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I37.13-1: R1= cyclohexyl, R2= methyl, R3= 4-N-(2-dimethylamino-ethyl)-N-methyl-benzamide

4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide

To a suspension of I37.13 (0.3 mmol, 100 mg) in dimethylformamide (1 ml), sodium hydride at 60% dispersion in mineral oil (0.6 mmol, 24 mg), 2-dimethylaminoethylchloride hydrochloride (0.36 mmol, 52 mg) and K_2CO_3 (0.36 mmol, 50 mg) were added. The mixture was stirred overnight at 40°C. Then, potassium ter-butoxyde (0.18 mmol, 20 mg) was added and the mixture was stirred during 24H. 2-dimethylaminoethylchloride hydrochloride (0.18 mmol, 26 mg), and K_2CO_3 (0.18 mmol, 25 mg) were added and

warmed at 40°C overnight. The mixture was reduce under pressure vacuum to give a residue which was purified by silica gel chromatography, eluting with a gradient of dicloromethane containing from 0 to 6% methanol to aff rd the title product.

Yield: 16%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.00 (s, 3H), 2.25 (s, 3H), 2.30-2.40 (m, 1H), 2.60-2.70 (m, 1H), 2.88-3.02 (m, 3H), 3.55 (s, 3H), 7.45 (dd, 2H), 7.70 (dd, 2H).

MS (m/z) / M+1= 402

HPLC (uv purity, λ = 214 nm)= 98.8%

Example I37.14: R1= cyclohexyl, R2= methyl, R3= 4-(3-hydroxy-methyl-piperidin-1-carbonyl)-phenyl [4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone

Compound I37.14 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, t give the desired product.

Yield: 34%

^{1}H-NMR (350K, 400MHz, DMSO) δ ppm: 1.20-1.50 (m, 7H), 1.50-1.70 (m, 3H), 1.70-1.85 (m, 5H), 2.63-2.78 (m, 2H), 2.88-2.98 (m, 1H), 3.18-3.28 (m, 1H), 3.28-3.38 (m, 1H), 3.50 (s, 3H), 3.75-4.10 (m, 2H), 4.18-4.28 (m, 1H), 7.45 (dd, 2H), 7.68 (dd, 2H).

MS (m/z) / M+1= 415

HPLC (uv purity, λ= 214 nm)= 95.4%

Example I37.15: R1= cyclohexyl, R2= methyl, R3= 4-{N-[(S)-1-tert-butoxycarbonyl-2-(4-hydroxy-phenyl)-ethyl]}benzamide 2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester

Compound I37.15 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 2% methanol and then the product was washed with water, extracted with ethylacetate and the organic layer was washed with brine, dried over magnesium sulfate and reduced under pressure vacuum to give the title product.

Yield: 70%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 14H), 1.55-1.65 (m, 1H), 1.70-1.80 (m, 4H), 2.58-2.68 (m, 1H), 2.91-3.01 (m, 2H), 3.52 (s, 3H), 4.45-4.51 (m, 1H), 6.65 (dd, 2H), 7.08 (dd, 2H), 7.71 (dd, 2H), 7.90 (dd, 2H), 8.75 (d, 1H), 9.15 (s, 1H).

MS (m/z) / M+1= 537

HPLC (uv purity, λ= 214 nm)= 96.3%

Example I37.15-a: R1= cyclohexyl, R2= methyl, R3= 4-[N-((S)-1-carboxy-2-(4-hydroxy-phenyl)-ethyl)]benzamide

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid; compound with 2,2,2-trifluoro-acetic acid

To a solution of I37.15 (0.186 mmol, 100 mg) in dichloromethane (1.5 ml), trifluoroacetic acid (4.4 mmol, 378 µl) was added and the mixture was stirred at reflux during 2 hours. The mixture was purified by silica gel chromatography, eluting with a gradient of dicloromethane containing from 0 to 10% methanol to afford 60 mg of the title product.

Yield: 54%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.12-1.52 (m, 5H), 1.58-1.68 (m, 1H), 1.73-1.85 (m, 2H), 1.85-2.05 (m, 2H), 2.88-3.11 (m, 3H), 3.75 (s, 3H), 4.48-4.60 (m, 1H), 6.62 (dd, 2H), 7.08 (dd, 2H), 7.85 (dd, 2H), 7.95 (dd, 2H), 9.15 (s, 1H), 12.75 (s, 1H).

MS (m/z) / M+1= 481

HPLC (uv purity, λ= 214 nm)= 98%

Example I37.16: R1= cyclohexyl, R2= methyl, R3= 4-(N-((S)-1-tert-butoxycarbonyl)-ethyl)benzamide

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester

Compound I37.16 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 2% methanol, and the product was washed with water, filtrered and dried under pressure vacuum with P_2O_5 to give the title compound.

Yield: 65%

^{1}H-NMR (400MHz , DMSO) δ ppm: 1.20-1.40 (m, 17H), 1.55-1.65 (m, 1H), 1.70-1.82 (m, 4H), 2.58-2.68 (m, 1H), 3.52 (s, 3H), 4.35 (q, 1H), 7.73 (dd, 2H), 7.95 (dd, 2H), 8.75 (d, 1H).

MS (m/z) / M+1= 445

HPLC (uv purity, λ= 214 nm)= 99.3%

Example I37.16-a: R1= cyclohexyl, R2= methyl, R3= 4-(N-((S)-1-carboxy)-ethyl)benzamide

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid

To a solution of I37.16 (0.225 mmol, 100 mg) in dichloromethane (1 ml) at 0°C, trifluoroacetic acid (5.85 mmol, 457 µl) was added and the mixture was stirred at room temperature overnight. The mixture was purified by silica gel chromatography, eluting with a gradient of dicloromethane containing from 0 to 5% methanol to afford 40 mg of the title product.

Yield: 35%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.48 (m, 8H), 1.55-1.65 (m, 1H), 1.70-1.81 (m, 2H), 1.81-2.00 (m, 2H), 2.89-3.05 (m, 1H), 3.71 (s,3H), 4.44 (q, 1H), 7.87 (dd, 2H), 8.03 (dd, 2H), 8.82 (d, 1H), 12.57 (s, 1H).

MS (m/z) / M+1= 388/389

HPLC (uv purity, λ= 214 nm)= 97.9%

Example I37.17: R1= cyclohexyl, R2= methyl, R3= 4-(4-pyridin-2-yl-piperazine-1-carbonyl)-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone

Compound I37.17 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, and then the product was washed with water, filtered and dried under reduced pressure over P_2O_5 to give the desired product.

Yield: 82%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.48 (m, 5H), 1.55-1.65 (m, 1H), 1.70-2.00 (m, 4H), 2.62-2.92 (m, 1H), 3.35-3.87 (m, 11H), 6.67 (dd, 1H), 6.88 (d, 1H), 7.45-7.63 (m, 3H), 7.78 (dd, 2H), 8.12 (d, 1H).

MS (m/z) / M+1= 463

HPLC (uv purity, λ = 214 nm)= 99.9%

Example I37.18: R1= cyclohexyl, R2= methyl, R3= 4-[4-(4-fluoro-phenyl)-piperazine-1-carbonyl]-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone

Compound I37.18 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, and then the product was washed with water, filtred and dried under reduced pressure over P_2O_5 to give the desired product.

Yield: 31%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.65-1.86 (m, 4H), 2.56-2.70 (m, 1H), 2.96-3.10 (m,

4H), 3.37-3.85 (m, 7H), 6.67 (dd, 1H), 6.92-7.12 (m, 4H), 7.51 (dd, 2H), 7.71 (dd, 2H).
MS (m/z) / M+1= 480
HPLC (uv purity, λ= 214 nm)= 98.6%

Example I37.19: R1= cyclohexyl, R2= methyl, R3= 4-[N-(3,4,5-trimethoxy-benzyl)]-benzamide
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide

Compound I37.19 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.
The residue was purified by silica gel chromatography using a gradient of cyclohexane containing 0 to 30% ethylacetate, to give a product which was washed with water, filtred and dried under reduced pressure over P_2O_5 to give the desired product.
Yield: 52%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.19-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.71-1.88 (m, 4H), 2.60-2.70 (m, 1H), 3.50-3.55 (m, 3H), 3.55 (s, 3H), 3.75 (s, 6H), 4.42 (d, 2H), 6.65 (s, 4H), 7.70-7.80 (m, 1H), 8.00 (d, 1H), 9.10 (t, 1H).
MS (m/z) / M+1= 497
HPLC (uv purity, λ= 214 nm)= 99.5%

Example I37.20: R1= cyclohexyl, R2= methyl, R3= 4-(4-pyrimidin-2-yl-piperazin-1-carbonyl)-phenyl
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone

Compound I37.20 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.
The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 1% methanol, to give a product which was washed with water, filtred and dried under reduced pressure over P_2O_5 to give the desired product.
Yield: 4%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.41 (m, 5H), 1.55-1.65 (m, 1H), 1.68-1.75 (m, 4H), 2.55-2.70 (m, 1H), 3.00-3.90 (m, 11H), 6.65 (t, 1H), 6.88 (d, 1H), 7.50 (dd, 2H), 7.70 (dd, 2H), 8.38 (d, 2H).

MS (m/z) / M+1= 464

HPLC (uv purity, λ= 214 nm)= 97%

Example I37.21: R1= cyclohexyl, R2= methyl, R3= 4-(4-methyl-piperazine-1-carbonyl)-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone

Compound I37.21 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of of dichloromethane containing 0 to 10% methanol, to give a product which was washed with water, filtred and dried under reduced pressure over P_2O_5 to give the desired product.

Yield: 55%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.18-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.69-1.81 (m, 4H), 2.25 (s, 3H), 2.33-2.52 (m, 4H), 2.59-2.69 (m, 1H), 3.25-3.45 (m, 2H), 3.52 (s, 3H), 3.55-3.70 (m, 2H), 7.78 (dd, 2H), 7.71 (dd, 2H).

MS (m/z) / M+1= 400

HPLC (uv purity, λ= 214 nm)= 99.6%

Example I37.22: R1= cyclohexyl, R2= methyl, R3= 4-[N-(3-(4-methyl-piperazin-1-yl)-propyl)]benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide

Compound I37.22 was prepared by the procedure described in exemple I37.11 using I37.1 as a starting material.

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 10% methanol, to give a product which was stirred in diethylether, filtred and dried under reduced pressure over P_2O_5 t give the

desired pr duct.
Yield: 3.5%
^{1}H-NMR (400MHz, $CDCl^3$): δ ppm: 1.20-1.50 (m, 5H), 1.60-2.05 (m, 7H), 2.35 (s, 3H), 2.48-2.85 (m, 11H), 3.52-3.64 (m, 2H), 3.50 (s, 3H), 7.68 (dd, 2H), 7.87 (dd, 2H), 8.00-8.08 (m, 1H).
MS (m/z) / M+1= 457
HPLC (uv purity, λ= 214 nm)= 97.2%

Example I37.23: R1= cyclohexyl, R2= methyl, R3= 4-N-[(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide
To a solution of 2-(aminomethyl)-1-ethylpyrrolidine (7.5 mmol, 967 mg) in dichloroethane (10 ml) under nitrogen atmosphere, was added dropwise trimethylaluminium [2N] in toluene (7.5 mmol, 3.8 ml) and the mixture was stirred at room temperature during 2 hours. A solution of compound I37 (1.5 mmol, 500 mg) in dichloroethane (10 ml) was then added and the stirring was pursued at 65°C overnight. At room temperature, dichloromethane (30 ml) and water (50 ml) were added and the mixture was stirred several hours. The mixture was filtered through celite, extracted with dichloromethane, washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 10% methanol to afford the desired product.
Yield: 79%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.05 (t, 3H), 1.20-1.42 (m, 5H), 1.55-1.70 (m, 4H), 1.70-1.85 (m, 5H), 2.10-2.18 (m, 1H), 2.25-2.35 (m, 1H), 2.55-2.70 (m, 2H), 2.80-2.90 (m, 1H), 3.00-3.12 (m, 2H), 3.39-3.49 (m, 1H), 3.55 (s, 3H), 7.71 (dd, 2H), 7.92 (dd, 2H), 8.49 (t, 1H).
MS (m/z) / M+1= 428
HPLC (uv purity, λ= 214 nm)= 99.2%

Example I37.24: R1= cyclohexyl, R2= methyl, R3= 4-N-[(pyridin-3-ylmethyl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide

Compound I37.24 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 2-(aminoethyl)pyridine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 8% methanol to afford the desired product.

Yield: 34%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.55 (s, 3H), 4.50 (d, 2H), 7.35-7.40 (m, 1H), 7.70-7.80 (m, 3H), 8.00 (dd, 2H), 8.45-8.50 (m, 1H), 8.57 (s, 1H), 9.30 (t, 1H).

MS (m/z) / M+1= 408

HPLC (uv purity, λ= 214 nm)= 98.6%

Example I37.25: R1= cyclohexyl, R2= methyl, R3= 4-(N-benzyl)-benzamide

N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

Compound I37.25 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and benzylamine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 2% methanol to afford the desired product.

Yield: 34%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.65-1.85 (m, 4H), 2.55-2.70 (m, 1H), 3.52 (s, 3H), 4.48 (d, 2H), 7.19-7.39 (m, 5H), 7.72 (dd, 2H), 7.98 (dd, 2H), 9.13 (t, 1H)

MS (m/z) / M+1= 407

HPLC (uv purity, λ= 214 nm)= 99.2%

Example I37.26: R1= cyclohexyl, R2= methyl, R3= 4-[N-(1-

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¡Esta página no forma parte del folleto!

WO 02-28847

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Fecha: 11 de abril de 2002

Destino: Agente

Domicilio:

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the pamphlet!

WO 02-28847

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Date: 11 apr 2002

Destination: Agent

Address:

benzyl-piperidin-4-yl)]-benzamide
N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide
Compound I37.26 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 4-amino-1-benzylpiperidine).
The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 8% methanol to afford the desired product.
Yield: 50%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.53-1.65 (m, 3H), 1.70-1.83 (m, 6H), 1.97-2.07 (m, 2H), 2.70-2.80 (m, 1H), 2.77-2.87 (m, 2H), 3.47 (s, 2H), 3.55 (s, 3H), 3.70-3.85 (m, 1H), 7.22-7.35 (m, 5H), 7.70 (dd, 2H), 7.93 (dd, 2H), 8.35 (d, 1H).
MS (m/z) / M+1= 490
HPLC (uv purity, λ= 214 nm)= 96.4%

Example I37.27: R1= cyclohexyl, R2= methyl, R3= 4-[N-(2-ethyl-2H-pyrazol-3-yl)]-benzamide
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide
Compound I37.27 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 5-amino-1-ethylpyrazole).
The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 6% methanol and then the solid was stirred in diethylether during 15 min, filtered and dried under reduced pressure to give the title product.
Yield: 26%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 8H), 1.60-1.70 (m, 1H), 1.75-1.87 (m, 4H), 2.63-2.73 (m, 1H), 3.55 (s, 3H), 4.05 (q, 2H), 6.25 (d, 1H), 7.45 (d, 1H), 7.83 (dd, 2H), 8.10 (dd, 2H), 10.40 (s, 1H).
MS (m/z) / M+1= 411
HPLC (uv purity, λ= 214 nm)= 99.7%

Example I37.28: R1= cyclohexyl, R2= methyl, R3= 4-(2-morpholin-4-yl-ethyl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide

Compound I37.28 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and N-(2-aminoethyl)morpholine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 6% methanol and then the solid was stirred in diethylether during 15 min, filtered and dried under reduced pressure to give the title product.

Yield: 21%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.63 (m, 1H), 1.70-1.83 (m, 5H), 2.35-2.50 (m, 6H), 2.57-2.67 (m, 1H), 3.38 (q, 2H), 3.50 (s, 3H), 3.52-3.57 (m, 4H), 7.80 (dd, 2H), 7.90 (dd, 2H), 8.50 (t, 1H)

MS (m/z) / M+1= 430

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I37.28-1: R1= cyclohexyl, R2= methyl, R3= 4-[(N-cyano-N'-ethylmorpholine)-carboxyimidamine]-phenyl

[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of I37.28 (2.33 mmol, 1 g) in toluene (15 ml), Lawesson's reagent (4.65 mmol, 1.88 g) was added and the mixture was stirred overnight at reflux. After cooling at room temperature, the mixture was acidified with a solution of HCl at 5% (3.5 ml) then basified with a solution f $NaHCO_3$. The aqueous layer was extracted with ethylacetate and the combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography t give 4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N(2-morpholin-4-yl-ethyl)thiobenzamide.

Yield: 56%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.83 (m, 4H), 2.60-2.75 (m, 3H), 3.52 (s, 3H), 3.55-3.63 (m, 4H), 3.78 (t, 2H), 3.80-3.90 (m, 2H), 7.70 (dd, 2H), 7.82 (dd, 2H), 10.28 (t, 1H).

To a solution of 4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N(2-morpholin-4-yl-ethyl)thiobenzamide (1.12 mmol, 500 mg) in THF (20 ml), sodium hydride (60% dispersion in mineral oil, 1.12 mmol, 44 mg) was added and the mixture was warmed at reflux during one hour. After cooling at room temperature, methyl iodide (1.35 mmol, 84 µl) was added and the mixture was warmed 4 hours at reflux and then overnight at room temperature. The mixture was concentrated under reduced pressure to give a crude material which was solubilized in ethanol (50 ml). To this solution, cyanamide(1.8 mmol, 75 mg) and triethylamine (0.9 mmol, 125µl) were added and the mixture was stirred 2 days at reflux. Mercury(II)chloride (1.68 mmol, 457 mg) and cyanamide (2.35 mmol, 100 mg) were added and the reaction was allowed to stir 3 days at room temperature. The mixture was concentrated under reduced pressure and the residue was diluted in ethyl acetate and filtered through celite. The filtrate was concentrated under vacuum. The residue was chromatographed on silica gel using a gradient of dichloromethane containing from 0 to 5% methanol to afford the title compound.

Yield: 17%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.18-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.40-2.50(m, 4H); 2.50-2.60(m, 2H), 2.60-2.70 (m, 1H), 3.45-3.55(m, 2H), 3.55 (s, 3H), 3.55-3.65(m, 4H), 7.68 (dd, 2H), 7.52 (dd, 2H), 9.15 (t, 1H).

MS (m/z) / M+1= 454

HPLC (uv purity, λ= 214 nm) = 95%

Example I37.29: R1= cyclohexyl, R2= methyl, R3= 4-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

Compound I37.29 was prepared by the procedure described in example I37.23 using appropriate intermediates and reagents (I37 and 1-(2-aminoethyl)pyrolidine).

The residue was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 14% methanol to afford the desired product.

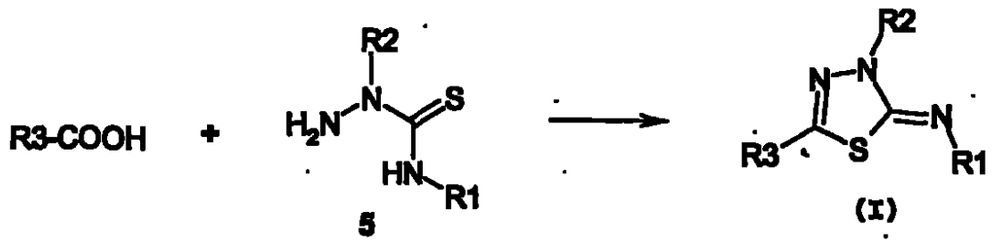
Yield: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.60-1.87 (m, 9H), 2.45-2.70 (m, 7H), 3.35-3.45 (m, 2H), 3.60 (s, 3H), 7.73 (dd, 2H), 7.95 (dd, 2H), 8.55 (t, 1H).

MS (m/z) / M+1= 414

HPLC (uv purity, λ= 214 nm)= 99.9%

Protocol D :



EXAMPLE I: PROTOCOL D

Example I15: R1= cyclohexyl, R2= methyl, R3= 4-methylsulfonyl-phenyl

Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

To a mixture of 4-methylsulfonyl-benzoic acid (2.5 mmol, 500 mg), 2-methylthiosemicarbazide 5a (2.5 mmol, 468 mg) in anhydrous dioxane (5 mL) at 65°C, $POCl_3$ (3 mmol, 280 μl) was added and the mixture was warmed at 95°C for 5 hours. The s lvent was removed by distillation under reduced pressure t give a crude material which was basified at pH 8-7 with a saturated solution f $NaHCO_3$. The aqueous phase was

extracted with dichoromethane. The rganic layer was washed with saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography (eluted with a gradient of cyclohexane/ethyl acetate finishing with the ratio 80/20) to afford 230 mg of the title compound.

Yield: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.25-1.45 (m, 5H), 1.65-1.75 (m, 1H), 1.75-1.95 (m, 4H), 1.70-1.80 (m, 1H), 3.35 (s, 3H), 3.65(s, 3H), 8.05(dd, 4H).

MS (m/z) / M+1= 352.5

HPLC (uv purity, λ= 214 nm): 95.3%

The compounds of the following examples were prepared by the procedure described in example I15 using appropriate intermediates and reagents:

I15.1	[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine
I15.2	Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Example I38: R1= cyclohexyl, R2= Me, R3= 3-pyridyl

Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine

Compound I38 was prepared by the procedure described in example I15 (protocol D) using appropriate intermediates and reagents.

The title product was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 10% ethylacetate.

Yield= 0.06 g, 13.5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.44 (m, 5H), 1.59-1.64 (b, 1H), 1.73-1.83 (b, 4H), 2.61-2.70 (b, 1H), 3.54 (s, 3H), 7.50-7.53 (m, 1H), 8.04 (d, 1H), 8.63-8.67 (m, 1H), 8.85 (s, 1H).

MS (m/z) / M+1= 275/276

HPLC (uv purity, λ= 214 nm)= 95.87%

Example I39: R1= cyclohexyl, R2= methyl, R3= 3-sulfamoyl-phenyl

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

Compound I39 was prepared by the procedure described in example I15 (protocol D) using appropriate intermediates and reagents.

The title product was isolated by chromatography on silica gel eluting with dichloromethane containing from 0 t 5% methanol.

Yield= 8.0 %

^{1}H-NMR (400MHz, DMSO) δppm: 1.18-1.41 (m, 5H), 1.58-1.63 (m, 1H), 1.73-1.84 (m, 4H), 2.60-2.67 (m, 1H), 3.56 (s, 3H), 7.48 (s, 2H), 7.67 (t, 1H), 7.82-7.90 (m, 2H), 8.12 (s, 1H).

MS (m/z) / M+1= 353/354

HPLC (uv purity, λ= 214 nm)= 97.55%

Example I40: R1= cyclohexyl, R2= methyl, R3= benzo[1,3]dioxol-5-yl

(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine

Compound I40 was prepared by the procedure described in example I15 (protocol D) using appropriate intermediates and reagents.

The title product was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 15% ethylacetate.

Yield: 27%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.45 (m, 5H), 1.60-1.70 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.70 (m, 1H), 3.50 (s, 3H), 6.15 (s, 2H), 7.00 (d, 1H), 7.15 (d, 1H), 7.25 (s, 1H)

MS (m/z) / M+1= 318

HPLC (uv purity, λ= 214 nm): 99.9%

Example I41: R1= cyclohexyl, R2= methyl, R3= 3,4,5-trimethoxyphenyl

Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine

Compound I41 was prepared by the procedure described in example I15 (protocol D) using appropriate intermediates and reagents.

The title product was isolated by chromatography on silica gel eluting with heptane containing from 0 to 20% diethylether.

Yield: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.50 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.65-2.70 (m, 1H), 3.50 (s, 3H), 3.70 (s, 3H), 3.85 (s, 6H), 6.90 (s, 2H)

MS (m/z) / M+1= 364.49

HPLC (uv purity, λ= 214 nm): 99.9%

EXAMPLE I: PROTOCOL A

Example I42 : R1= cyclopentyl, R2= methyl, R3= 4-cyano-phenyl

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

To a suspension of 1,3,4-thiadiazolium perchlorate (3c) (0.86 mmol, 300 mg) in ethanol (20 ml), cyclopentylamine (1.03 mmol, 102 µl) and triethylamine (1.03 mmol, 264 µl) were added, and the mixture was stirred at reflux overnight. The mixture was concentrated by distillation of the solvent and the crude material was solubilized in ethyl acetate. The inorganic salts were removed by extraction with water. The organic layer was washed with water and a solution of NaCl, dried under magnesium sulphate, filtered, and distilled to give a residue which was chromatographed on silica gel column (using a gradient of solvent ethyl acetate-cyclohexane starting with a ratio 0/100 to 20/80) to is late 210 mg f the pure product.

Yield= 85.7%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.40-1.95 (m, 8H), 3.15-3.25 (m, 1H), 3.50 (s, 3H), 7.80 (dd, 2H), 7.92 (dd, 2H).
MS (m/z) / M+1= 285

Example I43: R1= cycloheptyl, R2 = methyl, R3= 4-cyanophenyl
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile
The compound I43 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 20% ethylacetate.
Yield= 70.6%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.40-1.85 (m, 12H), 2.75-2.85 (m, 1H), 3.50 (s, 3H), 7.80 (dd, 2H), 7.90 (dd, 2H).
MS (m/z) / M+1= 313

Example I44: R1= 4-fluorophenyl, R2= Methyl, R3= 4-cyano-phenyl
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
The compound I44 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 20% ethylacetate.
Yield= 71.1%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.72 (s, 3H), 7.03-7.10 (m, 2H), 7.16-7.25 (m, 2H), 7.83 (dd, 2H), 7.93 (dd,2H).
MS (m/z) / M+1= 311

Example I45: R1= 3-phenol, R2= methyl, R3= 4-cyano-phenyl
4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
The compound I45 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (prot c l A). The residue was purified by chromatography on

silica gel eluting with a gradient of dichloromethane containing from 0 to 20% methanol.
Yield = 99%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.70 (s, 3H), 6.41-6.55 (m, 3H), 7.15 (t, 1H), 7.82 (dd, 2H), 7.91 (dd,2H), 9.42 (s, 1H).
MS (m/z) / M+1= 309

Example I46: R1= 4-fluoro-3-benzoic acid, R2= methyl, R3= 4-cyano-phenyl
5-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid
The compound I46 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). In this particular case, the residue was precipitated in ethylacetate to afford the pure product.
Yield= 65.5%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.74 (s, 3H), 7.24-7.37 (m, 3H), 7.44-7.51 (m, 1H), 7.85 (dd, 2H), 7.94 (dd,2H), 13.31 (b, 1H).
MS (m/z) / M+1= 355

Example I47: R1= 4-methyl-cyclohexyl, R2= methyl; R3= 4-cyano-phenyl
I47a : 4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
I47b : 4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile
The compound I47 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 20% ethylacetate to give the cis and trans isomers.
Yield= 68.6%
Compound cis: I47a

^{1}H-NMR (400MHz, DMSO) δ ppm: 0.92 (d, 3H), 1.38-1.68 (m, 9H), 2.85-2.92 (m, 1H), 3.55 (s, 3H), 7.80 (dd, 2H), 7.92. (dd, 2H).
MS (m/z) / M+1= 313

Compound trans:I47b

^{1}H-NMR (400MHz, DMSO) δ ppm: 0.88 (d, 3H), 0.94-1.09 (m, 2H), 1.30-1.45 (m, 3H), 1.64-1.83 (m, 4H), 2.48-2.60 (m, 1H), 3.52 (s, 3H), 7.80 (dd, 2H), 7.92 (dd, 2H).
MS (m/z) / M+1= 313

Example I48: R1= trans-4-hydroxycyclohexyl, R2= methyl, R3= 4-cyano-phenyl

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compound I48 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). Using 0.86 mmol of thiadiazolium, an excess of trans-4-aminocyclohexanol hydrochloride (7.7 mmol) and 8.6 mmol of triethylamine. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 30% ethylacetate.
Yield= 74%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.18-1.42 (m,4H), 1.73-1.89 (m,4H), 2.52-2.62 (m,1H), 3.40-3.50(m,1H), 3.53 (s, 3H), 4.50 (s, 1H), 7.80 (dd, 2H), 7.92 (dd, 2H).
MS (m/z) / M+1= 315
HPLC (uv purity, λ= 214 nm)= 99.9%

Example I49: R1= exo-2-norbornyl, R2= methyl, R3= 4-cyano-phenyl

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compound I49 was prepared by the procedure described in example I48 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cycl hexane containing from 0 t 8% ethylacetate.

Yield= 64%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.20 (m, 3H), 1.26-1.35 (m, 1H), 1.40-1.53 (m, 2H), 1.56-1.61 (m, 1H), 1.70-1.79 (m, 1H), 2.09-2.14 (m, 1H), 2.24-2.29 (m, 1H), 2.71-2.78 (m, 1H), 3.52 (s, 3H), 7.80 (dd, 2H), 7.91 (dd, 2H).

MS (m/z) / M+1= 311

HPLC (uv purity, λ= 214 nm)= 99.2%

Example I50: R1= (1R*, 2R*)-2-hydroxy-cyclohexyl, R2= methyl, R3= 4-cyano-phenyl

4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compound I50 was prepared by the procedure described in example I48 using the appropriate intermediates and reagents (protocol A). The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 50% ethylacetate.

Yield= 74%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.58-1.75 (m, 3H), 1.80-1.90 (m, 1H), 2.38-2.49 (m, 1H), 3.30-3.40 (m, 1H), 3.55 (s, 3H), 4.50 (s, 1H), 7.80 (dd, 2H), 7.92 (dd, 2H).

MS (m/z) / M+1= 315

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I51: R1= (1R*, 2S*)-2-hydroxycyclohexyl, R2= methyl, R3= 4-cyano-phenyl

4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

Compound I51 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). 1,3,4-thiadiazolium perchlorate (0.287 mmol, 100 mg) in ethanol (6 ml), cis-2-aminocyclohexanol hydrocloride (2.58 mmol, 390 mg) and triethylamine (2.87 mmol, 400 µl) were added. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 30% ethylacetate.

Yield= 72%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.80 (m, 8H), 2.83-2.97 (m, 1H),3.52-3.70 (m, 4H), 4.10-4.20 (m, 1H), 7.80 (dd, 2H), 7.94 (dd, 2H).

MS (m/z) / M+1= 315

HPLC (uv purity, λ = 214 nm)= 98.7%

Examples I52-a and I52-b : R1= 3-hydroxycyclohexyl, R2= methyl, R3= 4-cyano-phenyl

I52-a: 4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

I52-b: 4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

The compounds I52-a and I52-b were prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). A mixture of 1,3,4-thiadiazolium perchlorate (3c) (3.5 mmol, 1.22 g) in ethanol (80 ml), racemic-3-aminocyclohexanol (4.2 mmol, 485 mg) and triethylamine (4.2 mmol, 587 µl) was stirred at reflux during 4H. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 60% ethylacetate to give 120 mg of the trans isomer and 260 mg cis isomer.

1R*, 3R* isomer (I52a)

Yield = 11%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.35-1.50 (m, 2H), 1.50-1.70 (m, 6H),3.04-3.12 (m, 1H), 3.54 (s, 3H), 3.88-3.96 (m, 1H), 4.44 (d, 1H), 7.80 (dd, 2H), 7.94 (dd, 2H).

1R*, 3S* isomer (I52b)

^{1}H (400MHz, DMSO) δ ppm: 1.03-1.30 (m, 4H), 1.64-1.78 (m, 2H),1.78-1.87 (m, 1H), 1.98-2.04 (m, 1H), 2.58-2.70 (m, 1H), 3.40-3.58 (m, 4H), 4.61 (s, 1H), 7.44 (s, 1H), 7.70 (dd, 2H), 7.95 (dd, 2H), 8.07 (s, 1H).

Example I53: R1= (1R*, 3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-(methylsulfonyl)phenyl

(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidenamino]-cyclohexanol

The compound I53 was prepared by the procedure described in example I42 using the appropriate intermediates and reagents (protocol A). A mixture of 1,3,4-thiadiazolium perchlorate (3b) (1 mmol, 400 mg), ethanol (25 ml), 3-aminocyclohexanol (1.2 mmol, 140 mg) and triethylamine (2.5 mmol, 350 µl) was stirred at reflux during 3H. The residue was purified by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 to 50% ethylacetate. The product was then purified by HPLC on Kromasil C18 column with a gradient of acetonitrile/water 95/5 to 5/95 to give the pure product.

Yield= 10%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.30-1.69 (m, 8H), 3.00-3.10 (m, 1H), 3.21 (s, 3H), 3.52 (s, 3H), 3.82-3.95 (m, 1H), 4.35 (d, 1H), 7.85 (dd, 2H), 7.98 (dd, 2H)

MS (m/z) / M+1= 367/369

HPLC (uv purity, λ= 214 nm)= 98.9%

Example I54: R1= (1R*, 3R*)-3-Hydroxy-cyclohexyl, R2= methyl, R3= 4-benzoic acid

4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid

To a solution of I52a (3.18 mmol, 1 g) in isopropanol (20ml), a solution of KOH [6N] (15.9 mmol, 2.6 ml) was added and the mixture was stirred at reflux during 4 days. The mixture was acidified to pH= 6-7 with a solution of HCl and concentrated under reduced pressure to give the carboxylic acid derivative I54.

1H (400MHz, DMSO) δ ppm : 1.32-1.70(m, 8H), 3.03-3.12 (m, 1H), 3.50 (s, 3H), 3.85-3.95 (m, 1H), 4.35-4.50 (m, 1H), 7.75 (dd, 2H), 8.00 (dd,2H), 13.15 (s, 1H)

Example I55: R1= (1R*, 3R*)-3-hydroxycyclohexyl, R2= methyl, R3= 4-[N-(2-morpholin-4-yl-ethyl)]benzamide

4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide

Compound I55 was prepared by the procedure described in exemple I37.11 using I54 as a starting material.

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 4% methanol, to give the desired product.

Yield: 14%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.35-1.70 (m, 8H), 2.35-2.52 (m, 6H), 3.02-3.12 (m, 1H), 3.32-3.45 (m, 2H), 3.50-3.62 (m, 7H), 3.88-3.95 (m, 1H), 4.40 (d, 1H) 7.72 (dd, 2H), 7.92 (dd, 2H), 8.50 (s, 1H).

MS (m/z) / M+1= 446

HPLC (uv purity, λ= 214 nm)= 96.6%

Example I56: R1= trans-4-hydroxycyclohexyl, R2 = methyl, R3= 4-benzoic acid

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid

To a solution of I48 (1.9 mmol, 600 mg) in ethanol (15 ml) and isopropanol (15 ml),a solution of KOH [6N] (5.7 mmol, 960 µl) was added and stirred at reflux during 7H. The mixture was acidified to pH = 6-7 with a solution of HCl and then concentrated under reduced to give the carboxylic acid derivative I56.

^{1}H-RMN (400MHz, DMSO) δ ppm: 1.22-1.32 (m, 2H), 1.60-1.80 (b, 2H), 1.90-2.04 (m, 4H), 3.41-3.50 (m, 1H), 4.00 (s, 3H), 7.80-7.90 (m, 2H), 8.00-8.10 (m, 2H), 11.00 (s, 1H).

Example I57: R1= trans-4-hydroxy-cyclohexyl, R2= methyl, R3= 4-(N-2-hydroxy-1,1-dimethyl-ethyl)benzamide

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

Compound I57 was prepared by the procedure described in exemple I37.11 using I56 as a starting material.The residue

was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 9% methanol, to give the expected product.

Yield: 20%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.15-1.45 (m, 10H), 1.70-1.90 (m, 4H), 2.50-2.60 (m, 1H), 3.40-3.55 (m, 6H), 4.50 (d, 1H) 4.85 (d, 1H), 7.60 (s, 1H), 7.70 (dd, 2H), 7.89 (dd, 2H).

MS (m/z) / M+1= 405

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I58: R1= (1R*, 3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-(N-2-hydroxy-1,1-dimethyl-ethyl)benzamide

4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

Compound I58 was prepared by the procedure described in example I55 using appropriate intermediates and reagents (I54 and 1,1-dimethyl-2-ethanolamine).

The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 5% methanol, to give the desired product.

Yield: 58%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.20-1.70 (m, 14H), 3.02-3.12 (m, 1H), 3.40-3.60 (m, 5H), 3.85-3.95 (m, 1H), 4.40 (d, 1H), 4.85 (d, 1H), 7.60 (s, 1H), 7.68 (dd, 2H), 7.85 (dd, 2H)

MS (m/z) / M+1= 405

HPLC (uv purity, λ= 214 nm)= 94.4%

Example I59: (1R*, 3R*)-3-hydroxycyclohexyl, R2= methyl, R3= 4-(N-tert-butyl)-benzamide

N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I59 was prepared by the procedure described in example I55 using appropriate intermediates and reagents (I54 and isobutylamine). The residue was purified by silica gel chromatography using a gradient f dichloromethane containing 0 to 10%.

Yield: 33%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.30-1.70 (m, 17H), 3.02-3.12 (m, 1H), 3.50 (s, 3H), 3.85-3.95 (m, 1H), 4.40 (d, 1H), 7.68 (dd, 2H), 7.80-7.90 (m, 3H).

MS (m/z) / M+1= 389

HPLC (uv purity, λ= 214 nm)= 94.1%

Example I60: R1= (1R*, 3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-[N-(1,1-dimethyl-3-oxo-butyl)]-benzamide

N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a suspension of diacetoamine hydrogenoxalate (3 mmol, 616 mg) in DMF (6 ml) under nitrogen atmosphere, morpholine resin [3.47 mmol/g] (7 mmol, 2 g) was added, and the mixture was stirred at room temperature during 30 minutes and then filtered. A mixture of acid I54 (0.6 mmol), the filtrate, N,N-diisopropylethylamine(1.32 mmol, 227 µl), benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (0.72 mmol, 318 mg), 1-hydroxy-7-azabenzotriazole (0.3 mmol, 82 mg) was stirred at room temperature during 4H. The mixture was concentrated and then diluted in dichloromethane. The organic layer was washed with a satured solution of ammonium chloride, a satured solution of $NaHCO_3$, with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a gradient of dichloromethane containing 0 to 8% methanol. The compound was purified by HPLC (Kromasil C18 column) eluting with acetonitrile/water 95/5 to 5/95 to give the desired product.

Yield: 10%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.30-1.70 (m, 14H), 2.05 (s, 3H), 2.92-3.10 (m, 3H), 3.50 (s, 3H), 3.85-3.95 (m, 1H), 4.40 (d, 1H), 7.68 (dd, 2H), 7.85 (dd, 2H), 7.95 (s, 1H).

MS (m/z) / M+1= 431

HPLC (uv purity, λ= 214 nm)= 99.3%

Example I61: R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-[N-(2-cyano-1,2,2-trimethyl-ethyl)]-benzamide

N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I61 was prepared by the procedure described in example I55 using appropriate intermediates and reagents (I54 and 2-amino-2,3-dimethylbutanenitrile).

The residue was purified by silica gel chromatography using a gradient of cyclohexane containing 0 to 70% ethylacetate, to give the title product.

Yield: 8%

^{1}H-NMR (400MHz, DMSO): δ ppm: 0.95 (d, 3H), 1.10 (d, 3H), 1.30-1.70 (m, 11H), 2.45-2.65 (m, 1H), 3.00-3.10 (m, 1H), 3.50 (s, 3H), 3.85-3.95 (m, 1H), 4.40 (d, 1H), 7.70 (dd, 2H), 7.90 (d, 2H), 8.65 (s, 1H).

MS (m/z) / M+1= 428

HPLC (uv purity, λ= 214 nm)= 99.4%

Example I62: R1= (1R*, 3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-(N-1-methoxycarbonyl-cyclopropyl)-benzamide

1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester

Compound I62 was prepared by the procedure described in example I37.24 using appropriate intermediates and reagents (I55 and 1-aminocyclopropane-1-carboxylic acid, methylester hydrochloride)

The residue was purified once by silica gel chromatography using a gradient of dichloromethane containing 0 to 10% methanol and by HPLC (Hypersil Column) with a gradient acetonitrile/water 95/5 to 5/95 to afford the desired product.

Yield: 32%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1.12-1.20 (m, 2H), 1.33-1.50 (m, 4H), 1.50-1.70 (m, 6H), 3.03-3.12 (m, 1H), 3.52 (s, 3H),

3.60 (s, 1H), 3.89-3.98 (m, 1H), 4.40 (d, 1H), 7.72 (dd, 2H), 7.94 (d, 2H), 9.17 (s, 1H).
MS (m/z) / M+1= 431
HPLC (uv purity, λ= 214 nm)= 97.9%

Example I63: R1= cyclopentyl, R2= methyl, R3= 4-benzamide
4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-benzamide

To a solution of compound I42 (0.53 mmol, 150 mg) in ethanol (17 ml), a solution of Na_2CO_3 [3N] (5.6 mmol, 1.88 ml) and a solution of H_2O_2 at 30% in water (1.54 ml) were added. The solution was stirred overnight at room temperature. To the mixture, was added a solution of H_2O_2 at 30% in water (770 µl) and the solution was allowed to stir at room temperature during two days (reaction to completion). The resultant mixture was concentrated by distillation of the solvent and the crude material was precipitated in water. The precipitate was filtered off, washed several times with water and dried to give the pure product.

Yield= 53.4%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.43-1.95 (m, 8H), 3.18-3.28 (m, 1H), 3.52 (s, 3H), 7.44 (s, 1H), 7.70 (dd, 2H), 7.95 (dd,2H), 8.05 (s, 1H).
MS (m/z) / M+1= 303
HPLC (uv purity, λ= 214 nm)= 98.04%

Example I64: R1= cycloheptyl, R2= methyl, R3= 4-benzamide
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

Compound I64 was prepared by the procedure described in example I63 using appropriate intermediates (I43) and reagents.
The precipitate was filtered, washed several times with water and dried to give the pure product.
Yield= 59.88%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.40-1.83 (m, 12H), 2.78-2.85 (m, 1H), 3.52 (s, 3H), 7.44 (s, 1H), 7.72 (dd, 2H), 7.97 (dd,2H), 8.07 (s, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ= 214 nm)= 98.98%

Example I65: R1= 4-fluoro-phenyl, R2= methyl, R3= 4-benzamide

4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I65 was prepared by the procedure described in example I63 using appropriate intermediates I44 and reagents.

The precipitate was filtered, washed several times with water and dried to give the pure product.

Yield= 72.43%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.72 (s, 3H), 7.02-7.40(m, 2H), 7.15-7.24 (m, 2H), 7.44 (s, 1H), 7.72 (dd, 2H), 7.95 (dd,2H), 8.05 (s, 1H).

MS (m/z) / M+1= 329

HPLC (uv purity, λ= 214 nm)= 97.7%

Example I66: R1= 3-hydroxy-phenyl, R2= methyl, R3= 4-benzamide

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I66 was prepared by the procedure described in example I63 using appropriate intermediates (I45) and reagents.

The precipitate was filtered, washed several times with water and dried to give the pure product.

Yield= 59.84%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.70 (s, 3H), 6.44-6.52 (m, 3H), 7.18 (t, 1H), 7.44 (s, 1H), 7.75 (dd, 2H), 7.97 (dd, 2H), 8.06 (s, 1H), 9.40 (s, 1H).

MS (m/z) / M+1= 327

HPLC (uv purity, λ= 214 nm)= 99.68%

Example I67: R1= 4-fluoro-3-benzoic acid, R2= methyl, R3= 4-benzamide

5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid

Compound I67 was prepared by the procedure described in example I63 using appropriate intermediate (I46) and reagents.

The precipitate was filtered, washed several times with water and dried to give the pure product.

Yield= 44.41%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.72 (s, 3H), 7.25-7.32 (m, 2H), 7.43-7.50 (m, 2H), 7.78 (dd, 2H), 7.95 (dd, 2H), 8.05 (s, 1H), 13.30 (b, 1H).

MS (m/z) / M+1= 373

HPLC (uv purity, λ = 214 nm)= 90.52%

Example I68: R1= trans-4-methyl-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I68 was prepared by the procedure described in example I63 using appropriate intermediates (I47b) and reagents.

The precipitate was filtered, washed several times with water and dried to give the pure product.

Yield= 52.53%

^{1}H-NMR (400MHz, DMSO) δ ppm: 0.90 (d, 3H), 0.95-1.08 (m, 2H), 1.30-1.45 (m, 3H), 1.67-1.85 (m, 4H), 2.50-2.60 (m, 1H), 3.52 (s, 3H), 7.44 (s, 1H), 7.72 (dd, 2H), 7.95 (dd, 2H), 8.05 (s, 1H).

MS (m/z) / M+1= 331

HPLC (uv purity, λ= 214 nm)= 99.7%

Example I69: R1= trans-4-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a suspension of I48 (0.477 mmol, 150 mg) in ethanol (17 ml), a solution of Na_2CO_3 [3N] (5.1 mmol, 1.7 ml) and a solution of H_2O_2 at 30% in water (1.4 ml) were added and the mixture was stirred overnight at room temperature. This mixture was poured into water before extraction with ethyl acetate. The organic layer was washed with water and with a saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give a residue wich was purified by silica gel chromatography (eluted with a gradient of dichloromethane/methanol 100/0 to 98/2) to afford the pure product.

Yield= 31%

^{1}H-NMR(400MHz, DMSO) δ ppm: 1.20-1.42 (m, 4H), 1.75-1.90 (m, 4H), 2.50-2.63 (m, 1H), 3.40-3.52 (m,1H), 3.50 (s, 3H), 4.55 (s,1H), 7.44 (s, 1H), 7.72 (dd, 2H), 7.98 (dd, 2H), 8.07 (s, 1H).

MS (m/z) / M+1= 332/333

HPLC (uv purity, λ= 214 nm)= 97.3%

Example I70: R1= bicyclo[2.2.1]hept-2-yl, R2= methyl, R3= 4-benzamide

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I70 was prepared by the procedure described in example I69 using appropriate intermediates (I49) and reagents.

The residue was purified by silica gel chromatography (eluted with a gradient of dichloromethane/methanol 100/0 to 90/10)to afford the desired product.

Yield= 66%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.25 (m,3H), 1.28-1.40 (m,1H), 1.40-1.67 (m,4H), 2.10-2.18 (m,1H), 2.25-2.32 (m,1H), (2.70-2.80 (m,1H), 3.52 (s, 3H), 7.50 (s, 1H), 7.72 (dd, 2H), 7.97 (dd, 2H), 8.10 (s, 1H).

MS (m/z) / M+1= 329

HPLC (uv purity, λ= 214 nm)= 99.9%

Example I71: R1= (1R*,2R*)-2-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,2R*)-2-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I71 was prepared by the procedure described in example I69 using appropriate intermediates (I50) and reagents.

The residue was purified by silica gel chromatography (eluted with a gradient of dichloromethane/methanol 100/0 t 90/10)to afford the pure product.

Yield= 44%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.39 (m, 4H), 1.60-1.75 (m, 3H), 1.80-1.90 (m,1H), 2.35-2.45 (m, 1H), 3.50 (s, 3H), 4.55 (s,1H), 7.50 (s, 1H), 7.72 (dd, 2H), 7.96 (dd, 2H), 8.05 (s, 1H).

MS (m/z). / M+1=333

HPLC (uv purity, λ= 214 nm)= 97.4%

Example I72: R1= (1R*,2S*)-2-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a suspension of I51 (0.16 mmol, 50 mg) in DMSO (100 µl), K_2CO_3 (0.022 mmol, 3 mg), a solution of H_2O_2 at 30% in water (20 µl) was added and the mixture was stirred overnight at room temperature. To this mixture, water was added and the solution was allowed to stir 15 minutes. The precipitate was filtered off and dried under reduced pressure to give the desired product.

Yield= 68%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.25-1.38 (m, 2H), 1.40-1.80 (m, 6H), 2.85-2.90 (m, 1H), 3.57 (s, 3H), 3.60-3.68 (m, 1H), 4.10 (d,1H), 7.40 (s, 1H), 7.70 (dd, 2H), 7.95 (dd, 2H), 8.05 (s, 1H).

MS (m/z) / M+1= 333

HPLC (uv purity, λ= 214 nm)= 98.8%

Example I73: R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I73 was prepared by the procedure described in example I69 using appropriate intermediates (I52-a) and reagents.

The mixture was concentrated under reduced pressure and stirred in water several hours, filtered and dried under vaccum to afford the desired product.

Yield= 70%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.30-1.70 (m, 8H), 3.10 (s, 1H), 3.52 (s, 3H), 3.93 (s,1H), 4.42 (d, 1H), 7.43 (s, 1H), 7.70 (dd, 2H), 7.96 (dd,2H), 8.05 (s, 1H).

MS (m/z) / M+1=333

HPLC (uv purity, λ= 214 nm)= 98.3%

Example I74: R1= (1R*,3S*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

Compound I74 was prepared by the procedure described in example I69 using appropriate intermediates (I52-b) and reagents.

The mixture was concentrated under reduced pressure and stirred in water several hours, filtered and dried under vaccum to afford the desired product.

Yield= 83%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.05-1.30 (m, 4H), 1.65-1.78 (m, 2H), 1.78-1.88 (m, 1H), 1.95-2.05 (m, 1H), 3.40-3.58 (m, 4H), 4.60 (s, 1H), 7.45 (s, 1H), 7.70 (dd, 2H), 7.95 (dd, 2H), 8.05 (s, 1H).

MS (m/z) / M+1=333

HPLC (uv purity, λ= 214 nm)= 99.4%

Example I74.1: R1= 3-oxo-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a solution of I74 (0.15 mmol, 50 mg) in dichloromethane (0.5 ml), tetrapropylammoniumperruthenate (0.5% mol, 3 mg), 4-methylmorpholine-N-oxide (0.22 mmol, 28 mg) and molecular sieve (500 mg/mol, 75 mg) were added and the mixture was stirred at room temperature overnight. The mixture was filtered through a pad of silica gel (eluted with dichloromethane/methanol 100/0 to 95/5), the filtrate was concentrated under reduced pressure and washed with diethylether to afford the pure product.

Yield= 18%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.63-1.82 (m, 2H), 1.89-2.10 (m, 2H), 2.21-2.50 (m, 4H), 3.15-3.30 (m, 1H), 3.52 (s, 3H), 7.45 (s, 1H), 7.70 (dd, 2H), 7.98 (dd, 2H), 8.08 (s, 1H).

MS (m/z) / M+1=331

HPLC (uv purity, λ= 214 nm)= 98.7%

Example I75: R1= 3,3-difluoro-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a solution of I52-b (0.318 mmol, 100 mg) in dichloromethane (1 ml) was added tetrapropylammonium perruthenate (0.5 %mol,6 mg), 4-methylmorpholine-N-oxide (0.477 mmol, 56 mg) and molecular sieve (500 mg/mol, 160 mg). The mixture was stirred at room temperature for 3H, filtered through silica gel (eluted with cyclohexane/ethyl acetate 100/0 to 60/40) and concentrated under reduced pressure to afford 4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

Yield = 90%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.60-1.80 (m, 2H), 1.87-2.10 (m, 2H), 2.21-2.30 (m, 3H), 2.55-2.60 (m, 1H), 3.15 (s, 1H), 3.52 (s, 3H), 7.82 (dd, 2H), 7.92 (dd, 2H).

To a solution of this ketone (0.288 mmol, 90 mg) in dichloromethane (0.5 ml), a solution of deoxo-fluor (0.49 mmol, 90 µl) in dichloromethane (1 ml) and ethanol (0.346 mmol, 5 µl) was added and the mixture was stirred overnight at room temperature. The mixture was poured into a satured solution of $NaHCO_3$ (pH=7), and the aqueous layer was extrated with dichloromethane. The organic layer was washed with water and brine, dried with magnesium sulfate, filtered and concentrated under reduced pressure to give a residue wich was purified by silica gel chromatography (eluted with a gradient of cyclohexane/ethyl acetate 100/0 to 80/20)t afford the pure di-fluoro compound : 4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile

Yield = 12%

^{1}H-RMN (400MHz, DMSO) δ ppm: 1.40-1.55 (m, 2H), 1.78-1.90 (m, 4H), 1.95-2.09 (m, 1H), 2.15-2.28 (m, 1H), 2.80-2.90 (m, 1H), 3.55 (s, 3H), 7.82 (dd, 2H), 7.92 (dd, 2H).

To a solution of this di-fluoro derivative (0.036 mmol, 12 mg) in ethanol (1.6 ml) a solution of Na_2CO_3 [3N] (0.6 mmol, 200 µl), and a solution of H_2O_2 at 30% in water (150µl) were added and the mixture was stirred at 40°C overnight. Then, a solution of H_2O_2 at 30% in water (130 µl) was added and the solution was allowed to stir 12 h at 40°C. The mixture was concentrated under reduced pressure. The residue was stirred in water several hours, filtered, washed with ether and dried under vaccum to give the desired compound.

Yield= 40%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.33-1.53 (m, 2H), 1.70-1.90 (m, 4H), 1.90-2.05 (m, 1H), 2.15-2.28 (m, 1H), 2.80-2.90 (m, 1H), 3.55 (s, 3H), 7.48 (s, 1H), 7.72 (dd, 2H), 7.96 (dd, 2H), 8.08 (s, 1H)

MS (m/z) / M+1=353

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HPLC (uv purity, λ = 214 nm) = 98.7%

Example I76: R1= (1R*,3R*)-3-fluoro-cyclohexyl, R2= methyl, R3= 4-benzamide

4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a solution of I52-b (1.59 mmol, 500 mg) in dichloromethane (4 ml), 4-morpholinisulfurtrifluoride (3.18 mmol, 390 µl) was added at -15°C dropwise under nitrogen atmosphere. The mixture was warmed at room temperature during 30 minutes and poured into a saturated solution f $NaHCO_3$ (pH=7). The aqueous phase was extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduce pressure to give a residue wich was purified by silica gel chromatography (eluted with a gradient of cyclohexane/ethyl acetate 100/0 to 70/30) t afford 4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile and a mono-fluoro intermediate (4-[5-((trans)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile):
Yield= 14%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.40-1.50 (m, 1H), 1.58-1.85 (m, 6H), 1.92-2.05 (m, 1H), 2.95-3.05 (m, 1H), 3.55 (s, 3H), 4.95 (d, 1H), 7.83 (dd, 2H), 7.95 (dd, 2H).

To a solution of this fluoro intermediate (0.2 mmol, 65 mg) in ethanol (8.7 ml) a solution of Na_2CO_3 [3N] (2.61 mmol, 870 µl) and a solution of H_2O_2 at 30% in water (705 µl) were added and the mixture was stirred overnight at 40°C. A solution of H_2O_2 at 30% in water (705 µl) was added and the reaction was allowed to stir for 10h at 40°C. The mixture was concentrated under reduced pressure. The residue was stirred in water several hours, filtered, washed with ether and dried under vaccum to give the title product I76.
Yield= 58%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.35-1.52 (m, 1H), 1.52-1.90 (m, 6H), 1.90-2.08 (m, 1H), 2.93-3.08 (m, 1H), 3.55 (s, 3H),

5.00 (d, 1H), 7.50 (s, 1H), 7.78 (dd, 2H), 7.99 (dd, 2H), 8.10 (s, 1H).

MS (m/z) / M+1= 335

HPLC (uv purity, λ= 214 nm)= 96.6%

Example I77: R1= 3-cyclohexene, R2= methyl, R3= 4-benzamide

4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide

To a solution of 4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile from protoc l I76 (0.94 mmol, 280 mg) in ethanol (41 ml), a solution of Na_2CO_3 [3N] (12.3 mmol, 4.1 ml), and a solution of H_2O_2 at 30% in water (3.33 ml) were added. The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was stirred in water several hours, filtered, and dried under vaccum to afford the pure product.

Yield= 64%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.48-1.65 (m, 1H), 1.72-2.35 (m, 5H), 2.82-2.92 (m, 1H), 3.55 (s, 3H), 5.65 (t, 2H), 7.50 (s, 1H), 7.71 (dd, 2H), 7.95 (dd, 2H), 8.09 (s, 1H)

MS (m/z) / M+1= 315

HPLC (uv purity, λ= 214 nm)= 96.1%

Example I78: R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-(1H-tetrazol-5-yl)-phenyl

(1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidenesmino}-cyclohexanol

To a solution of I52-a (1.27 mmol, 400 mg) in toluene (3 ml), sodium azide (1.65 mmol, 108 mg) and triethylamine hydrochloride (1.65 mmol, 228 mg) were added and the mixture was warmed at reflux during 24 hours. The reaction mixture was cooled at room temperature, acidified with a solution f HCl [0.1N], and then basified at pH=6-7 with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with dichloromethane and the organic layer was washed with a saturated s lution f NaCl, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The

residue was chromatographed on silica gel column using a gradient of dichloromethane containing from 0 to 20% methanol to afford the title compound.
Yield: 50%
^{1}H-NMR (400MHz, DMSO): δ ppm: 1.30-1.70 (m, 8H), 3.00-3.15 (m, 1H), 3.50 (s, 3H), 3.85-3.98 (m, 1H), 4.40 (s, 1H), 7.75 (dd, 2H), 8.10 (d, 2H).
MS (m/z) / M+1= 358
HPLC (uv purity, λ= 214 nm)= 99.9%

Example I79: R1= 3-(6-hydroxy)-benzoic acid, R2= methyl, R3= 4-chloro-phenyl
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid
The title compound was prepared by the procedure desribed in example I3 using ethanol as solvent and appropriate intermediates and reagents. The residue was twice chromatographed on silica gel eluting with dichloromethane containing from 0 to 7% of methanol. The isolated product was washed with water to afford the desired product.
Yield= 9.7%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.62 (s, 3H), 6.80 (t, 1H), 7.12 (d, 1H), 7.40-7.46 (m, 3H), 7.59 (d, 2H).
MS (m/z) / M+1 =362/364.
HPLC (uv purity, λ= 214 nm): 98.36%

Example I80 : R1= 3-benzoic acid, R2= methyl, R3= 4-cyano-phenyl
3-[5-(4-cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
A suspension of 1,3,4-thiadiazolium perchlorate (3c) (4.873 mmol, 1.70 g), 3-aminobenzoic acid (4.87 mmol, 0.668 g) and triethylamine (4.873 mmol, 0.679 ml) in ethanol (20 ml) was refluxed for 3.5h. On cooling, the solid formed was filtered off and washed with cold EtOH and ether. The solid was dried under reduced pressure to give 1.25 g of the expected compound.

Yield= 76.2%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.87 (s, 3H), 7.39-7.42 (m, 1H), 7.60-7.65 (m, 1H), 7.70 (s, 1H), 7.78-7.82 (m, 1H), 7.96-8.00 (d, 2H), 8.00-8.04 (d, 2H).

MS (m/z) / M+1 = 337/338

HPLC (uv purity, λ= 214 nm)= 93.22%

Example I80.1: R1= 3-benzoic acid, R2= methyl, R3= 4-benzamide

3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

Concentrated sulfuric acid (19.8 mmol, 1.06 ml) and water (0.13 ml) were respectively added, at 0°C, to I80 (0.595 mmol, 0.200 g) and the reaction mixture was heated at 80°C for 1h30. Then, ice was added to the mixture and the formed precipitate was filtered off and purified by chromatography on silica gel, eluting with a mixture of acetic acid/dicloromethane/methanol (1.5/85/13.5). The isolated product was triturated in methanol and the solid was filtered off and dried under vaccum to give the title product.

Yield=34%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3.76 (s, 3H), 7.30 (d, 1H), 7.46-7.55 (m, 2H), 7.62 (s, 1H), 7.67 (d, 1H), 7.80 (d, 2H), 7.99 (d, 2H), 8.09 (s, 1H), 12.90-13.02 (d, 1H).

MS (m/z) / M+1= 355/356

HPLC (uv purity, λ= 214 nm): 96.37%

Example I81: R1= 4-fluoro-3-benzoic acid, R2= methyl, R3= 4-(methylsulfonyl)-phenyl

2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I81 was prepared by the procedure described in example I4 (protocol A) with the appropriate reagents and using 1.0 eq of triethylamine. The reaction mixture was concentrated and the residue was purified by silica gel chromatography

eluting with dichloromethane and then a mixture of dichloromethane/ MeOH/AcOH (98 /1.8 /0.2).
Yield= 13%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.19 (s, 3H), 3.57 (s, 3H), 7.11-7.19 (m, 2H), 7.31-7.34 (m, 1H), 3.50 , 7.79 (d, 2H), 7.85 (d, 2H), 13.08-13.14 (b, 1H).
MS (m/z) / M+1 = 408/409
HPLC (uv purity, λ= 214 nm)= 98.3%

Example I82: R1= 3-carboxylic acid cyclohexyl, R2= methyl, R3= 4-(methylsulfonyl)-phenyl
3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid
I82 was prepared by the procedure described in example I4 with the appropriate reagents and using 1.0 eq of triethylamine. The mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by silica gel chromatography eluting with $CHCl_3$/MeOH (93/7) to afford 15 mg of the desired product.
Yield= 1.52%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.02-1.24 (m, 4H), 1.58-1.70 (m, 3H), 1.80-1.86 (m, 1H), 2.12-2.19 (m, 1H), 2.44-2.52 (m, 1H), 3.06 (s, 3H), 3.36 (s, 3H), 7.70 (d, 2H), 7.82 (d, 2H), 11.82-11.90 (b, 1H).
MS (m/z) / M+1 = 395/396
HPLC (uv purity, λ= 214 nm): 98.76%

Example I83: R1= piperidin-1-yl, R2= methyl, R3= 4-(methylsulfonyl)-phenyl
[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine
To a suspension of 1,3,4-thiadiazolium perchlorate (3b) (1.26 mmol, 0.5 g) in ethanol (6 ml) were added 1-aminopiperidine (2.5 mmol, 0.3 ml) then triethylamine (2.5 mmol, 0.4 ml) and the mixture was maintained at 70°C for 3 hours. The mixture was concentrated under reduced pressure. The residue was taken int dichloromethane, washed twice

with water, concentrated under reduced pressure and purified by chromatography on silica gel (99:1 DCM/MeOH) to give 0.2 g of the title compound.
Yield = 45%.
^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.46 (s, 2H),1.68-1.71 (m, 4H), 2.77 (s, 4H), 3.07 (s, 3H), 3.65 (s, 3H), 7.81-7.83 (dd, 2H), 7.95-7.97 (dd, 2H).
MS (m/z) / M+1= 353.46.
HPLC (uv purity,λ= 214 nm)= 97.4%

Example I84: R1= tetrahydro-pyran-4-yl, R2= methyl, R3= 4-(methylsulfonyl)-phenyl
[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiaz l-2-ylidene]-(tetrahydro-pyran-4-yl)-amine
To a suspension of 1,3,4-thiadiazolium perchlorate (3b) (0.7 mmol, 0.3 g) in ethanol (4 ml) were added 4-aminotetrahydropyran (1.4 mmol, 0.3 g) and triethylamine (3 mmol, 0.4 ml). The mixture was maintained for 3 hours at 70°C, concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and purified by chromatography on silica gel (99:1 DCM/MeOH) and washed with ethyl acetate and heptane to give 23 mg of the expected compound.
Yield= 30%.
^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.68-1.85 (m, 4H), 2.88-2.95 (m, 1H), 3.07 (s, 3H), 3.47-3.57 (m, 2H), 3.65 (s, 3H), 4.01-4.06(m, 2H), 7.81 (d, 2H), 7.97(d, 2H).
MS (m/z) / M+1= 354.03
HPLC (uv purity, λ= 214 nm)= 100%.

Example I85: R1= 3-benzoic acid, R2= methyl, R3= 4-acetylamino-phenyl
3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid
A suspension of 1,3,4-thiadiaz lium triflate (3d) (0.7 mmol, 0.3 g), triethylamine (2.1 mmol, 0.3 ml) and 3-

acetamidobenzoic acid (0.6 mmol, 0.077 g) in ethanol (20 ml) was refluxed overnight. The mixture was concentrated under reduced pressure, purified by chromatography on silica gel (95:5 DCM /MeOH) and washed with MeOH to give 0.01 g f a white solid.

Yield= 5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2.06 (s, 3H), 2.71 (s, 3H), 7.26 (d, 1H), 7.47 (t, 1H), 7.60-7.70 (m, 6H), 10.18 (s, 1H).

MS (m/z) / M+1=368.95

HPLC (uv purity, λ= 214 nm)= 98%

Example I86: R1= trans-4-hydroxy-cyclohexyl, R2= methyl, R3= 4-acetylamino-phenyl

N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

A mixture of trans-4-aminocyclohexanol (0.28 mmol, 0.04 g), triethylamine (0.39 mmol, 0.06 ml) and 3-methyl-2-methylthio[1,3,4]thiadiazolium triflate (3d) (0.14 mmol, 0.05 g) were refluxed in ethanol (1ml) overnight. The mixture was concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water, concentrated under reduced pressure and purified by chromatography on silica gel (95:5 DCM /MeOH) to give 0.014g f a white solid.

Yield= 30%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.23-1.38 (m, 4H), 1.76-1.86 (m, 4H), 2.06 (s, 3H), 2.45-2.60 (m, 1H), 4.52 (d, 1H), 3.38-3.44 (m, 1H), 3.47 (m, 3H), 7.58 (d, 2H), 7.68 (d, 2H), 10.15 (s, 1H).

MS (m/z) / M+1 = 346.87

HPLC (uv purity, λ= 214 nm)= 98.5%

Example I87: R1= (1R*,3S*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-acetylamino-phenyl

N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

I87 was prepared by the procedure described in example I86 (protocol A).

I87 was purified by chromatography on silica gel with AcOEt:Cyclohexane (80:20) and washed with MeOH to give 0.15g of the expected compound.

Yield= 20%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.10-1.30 (m, 4H), 1.55-2.00 (m, 4H), 2.10 (s, 3H), 2.60 (m, 1H), 3.50 (m, 1H), 3.50 (s, 3H), 4.6 (d, 1H), 7.60 (dd, 2H), 7.60 (dd, 2H), 10.15 (s,1H).

M+1 = 347.1

Example I88: R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-acetylamino-phenyl

N-{4-[5-((1R*,3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

To a suspension of I87 (0.4 mmol, 0.15 g) in DCM (2 ml) containing 4Å molecular sieves (0.216 g), N-methyl morpholine oxide (0.65 mmol, 0.76 g) under nitrogen atmosphere was added tetrapropylammonium perruthenate (10% mol equiv., 15 mg). The resulting mixture was stirred overnight, filtered, washed with methanol and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with DCM:MeOH (95:5) to give 0.1 g of a ketone intermediate: N-{4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide

Yield= 71%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.25 (m, 1H), 1.60-1.75 (m, 2H), 1.85-2 (m, 2H), 2.05 (s, 3H), 2.3 (m, 3H), 3.15 (m,1H), 3.5 (s, 3H), 7.55 (dd, 2H), 7.70 (dd, 2H), 10.15 (s,1H).

To a solution of this ketone intermediate (0.15 mmol, 0.05 g) in THF (2 ml) at -70°C under nitrogen atmosphere was added a 1M solution of L-Selectride in THF (0.2 mmol, 0.2 mL). The resulting mixture was allowed to warm up to room temperature over 1 hour, diluted with dichl romethane, washed with water and concentrated under reduced pressure.

The residue was purified by chromatography on silica gel with AcOEt:Cyclohexane (80:20) to give 30 mg of the expected product.

Yield= 60%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.25-1.30 (m, 3H), 1.72-1.78 (m, 5H),2.20 (s, 3H), 3.11-3.14 (m, 1H), 3.58 (s, 3H), 4.13 (m, 1H), 7.20 (s, 1H), 7.52-7.60 (m, 4H).

MS (m/z) / M+1= 347.21

HPLC (uv purity, λ= 214 nm)= 98%

Example I89 : R1= (1R*,3R*)-3-hydroxy-cyclohexyl, R2= methyl, R3= 4-acetylamino-pyridin-3-yl

***N*-{5-[5-((1R*,3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide**

The compound I89 was prepared by the procedure described in example I4 (protocol A).

To a suspension of 1,3,4-thiadiazolium perchlorate (3e) (0.5 mmol, 2 g) in ethanol (20 ml) were added triethylamine (1.5 mmol, 2 ml) followed by 3-aminocyclohexanol (0.8 mmol, 0.9 ml) and the mixture was maintained at 70°C overnight, concentrated under reduced pressure. The residue was taken into dichloromethane, washed twice with water, concentrated under reduced pressure and purified by chromatography on silica gel (20:80 cyclohexane /EtOAc) to give 0.03g of a white solid.

Yield= 17%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.37-1.65 (m, 8H), 2.11 (s, 3H), 3.03-308 (m, 1H), 3.50 (s, 3H), 3.91-3.92 (m, 1H), 4.41 (d, 1H), 8.01-8.03 (dd, 1H), 8.17 (d, 1H), 8.55 (d, 1H), 10.75 (s, 1H).

MS (m/z) / M+1= 348.3

HPLC (uv purity, λ= 214 nm)= 99.2%

Example I90: R1= 3-cyano-phenyl, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile

To a suspension of I6.11 (4.14 mmol, 1.43 g) in pyridin (20 mL) was added benzoyl chloride (8.28 mmol, 964 µL). The mixture was heated at reflux for 2 days.

The solvent was concentrated under reduced pressure, the reaction mixture was retaken in an aqueous solution of $NaHCO_3$ and the crude product was extracted with dichloromethane. The compound was purified by chromatography on silica gel (eluted with cyclohexane/ethyl acetate: 80/20 to 70/30) to give 1.25 g of the expected compound (92%).

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.40 (d, 1H), 7.48 (s, 1H), 7.52-7.60 (m, 4H), 7.73 (d, 2H).

MS (m/z) / M+1= 327/329

HPLC (uv purity, λ= 245nm)= 99.4%

Example I90.1: R1= 3-(1H-Tetrazol-5-yl)-phenyl, R2= methyl, R3= 4-chloro-phenyl

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine

A mixture of I90 (1.22 mmol, 0.4 g), sodium azide (1.59 mmol, 0.1 g) and triethylamine hydrochloride (1.59 mmol, 0.22 g) in toluene (7 mL) was heated at 90°C with stirring under nitrogen atmosphere. After cooling, the reaction mixture was poured in water and extracted with dichloromethane. To the aqueous layer, aqueous HCl 0.1N was added until the pH is acidic (CAUTION! This has to be done under a well ventilated hood). The precipitate was filtered, washed with ether and the resulting compound was cristallized in dichloromethane containing few drops of methanol to give 0.1 g of the desired compound

Yield: 24%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.28 (d, 1H), 7.55 (d, 2H), 7.60 (t, 1H), 7.70-7.77 (m, 4H)

MS (m/z) / M+1 = 370/372

HPLC (uv purity, λ= 245 nm)= 99.7%

Example I90.2: R1= 3-(N-Hydroxycarbamimidoyl)-phenyl, R2= methyl, R3= 4-chloro-phenyl

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidenoamino]-N-hydroxy-benzamidine

To a mixture of I90 (1.53 mmol, 0.5 g) and hydroxylamine hydrochloride (2.29 mmol, 0.156 g) in ethanol (13 mL) was added sodium hydroxyde (2.29 mmol, 0.09 g) dissolved in the minimum of water. The reaction mixture was heated at reflux for 24h with stirring. After cooling, the precipitate is filtered, washed with ethanol and dried under vacuum at 45°C to give 0.54 g of the desired compound

Yield: 98%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 5.76 (bs, 2H), 7.05 (dd, 1H), 7.34-7.4 (m, 3H), 7.54 (d, 2H), 7.70 (d, 2H), 9.6 (s, 1H).

MS (m/z) / M+1= 360/362

HPLC (uv purity, λ= 245 nm)= 97.3%

Example I90.3: R1= 3-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-phenyl, R2= methyl, R3= 4-chloro-phenyl

3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidenoamino]-phenyl}-[1,2,4]oxadiazol-5-ol

A mixture of I90.2 (2.78 mmol, 0.1 g) and 1,1'-carbonyldiimidazole (5.56 mmol, 0.9 g) in anhydrous THF (2 mL) was heated at reflux for 5h. After cooling, the reaction mixture was concentrated and poured in water. Dichloromethane was added and the precipitate was filtered and washed with methanol. The resulting mixture was purified by chromatography on silica gel (eluent dichloromethane/methanol: 98/2 + 1% acetic acid) to give 0.03 g of the desired product.

Yield: 28%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.8 (s, 3H), 7.20 (dt, 1H), 7.50-7.55(m, 5H), 7.70 (d, 2H).

MS (m/z) / M+1 = 386/388

HPLC (uv purity, λ= 245 nm)= 98.2%

EXAMPLE I: PROTOCOL C

Example I91: R1= cyclohexyl, R2= methyl, R3= 3-methyl-4-bromo-phenyl

[5-(4-Bromo-3-methyl-phenyl)-3-methyl-3H-[1,3,4]thiadiaz 1-2-ylidene]-cyclohexyl-amine

I91 was prepared by the procedure described in example I18 (Protocol C)using appropriate intermediates and reagents.

Yield= 50.4 %

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.51 (m, 5H), 1.64-1.70 (m, 1H), 1.78-1.89 (m, 4H), 2.38 (s, 3H), 2.56-2.64 (m, 1H), 3.55 (s, 3H), 7.28 (d, 1H), 7.47 (s, 1H), 7.54 (d, 1H).

MS (m/z) / M+1= 366/368

Example I91.1: R1= cyclohexyl, R2= methyl, R3= 3-methyl-4-cyano-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-2-methyl-benzonitrile

To a solution of I91 (7.370 mmol, 2.7 g) in N-methyl-2-pyrrolidone (17ml), copper cyanide (13.267 mmol, 1.19 g) was added and the mixture was heated at reflux for 3h. The mixture was cooled at room temperature, basified with a solution of aqueous ammonia (2N) and stirred 10h at room temperature. The suspension was then filtered through Celite and the aqueous layer was extracted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a gradient of dichloromethane containing from 0 to 1% of methanol.

Yield= 54.8

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.22-1.59 (m, 5H), 1.64-1.67 (m, 1H), 1.77-1.87 (m, 4H), 2.57-2.67 (m, 4H), 3.60 (s, 3H), 7.52 (d, 1H), 7.56 (s, 1H), 7.63 (d, 1H).

Example I91.2: R1= cyclohexyl, R2= methyl, R3= 3-methyl-4-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide

To a solution of I91.1 (0.320 mmol, 0.1 g) in ethanol (17 ml), an aqueous solution of sodium carbonate 3N (3.424 mmol, 1.14 ml) then a solution of hydrogen peroxide (5.60 ml) were added. The suspension was stirred for 2 days at room temperature, then heated at 40°C for 8h. The mixture was poured into a solution of $Na_2S_2O_3$ and evaporated to dryness then the crude material was diluted with water and extracted with dicloromethane. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

Yield: 70%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.22-1.51 (m, 5H), 1.60-1.68 (m, 1H), 1.81-1.91 (m, 4H), 2.52 (s, 3H), 2.59-2.69 (m, 1H), 3.60 (m, 3H), 5.64-5.83 (b, 2H), 7.49 (s, 2H), 7.48 (s, 1H).

MS (m/z) / M+1= 331/332.

HPLC (uv purity, λ= 214 nm): 97.28%

Example I92: R1= cyclohexyl, R2= methyl, R3= 4-bromo-3-methoxy-phenyl

[5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine

To a mixture of 3-hydroxybenzoic acid (14.480 mmol, 2 g) in acetic acid (14.5 ml) and sulfuric acid (1.5 ml) at 50°C, a solution of bromine (15.204 mmol, 0.780 ml) in acetic acid (7.2 ml) was added and stirred 30 min at 100°C. The reaction was allowed to room temperature and diluted with water. The aqueous layer was extracted with ethylacetate, washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the 4-Bromo-2-hydroxy-benzoic acid (yield =100%).

To a solution of 4-bromo-3-hydroxybenzoic acid (14.480 mmol, 2.600 g) in acetone (180 ml), potassium carbonate (62.988 mmol, 8.710 g) and dimethylsulfate (31.422 mmol, 2.970 ml) were added. The reaction was stirred at room temperature f r 30 min and evaporated to dryness.The residue was then diluted with water and extracted with ethylacetate. The collected rganic layer was washed with water and brine,

dried ($MgSO_4$), filtered and concentrated under reduced pressure. 4-Bromo-3-methoxy-benzoic acid methyl ester was isolated by chromatography on silica gel eluting with cyclohexane containing from 0 to 20% ethylacetate (yield= 47%).

To a solution of 4-Bromo-3-methoxy-benzoic acid methyl ester (6.875 mmol, 1.676 ml) in a mixture 1/1 of THF/ MeOH (15ml), lithium hydroxyde (7.553 mmol, 0.180 g) was added and the reaction was stirred at room temperature overnight bef re distillation of volatiles. The residue was diluted with water, acidified with a solution of HCl (1N) and stirred for 1h. The formed precipitate was filtered off, washed with water and petroleum ether to give 4-Bromo-3-methoxy-benz ic acid (Yield = 56%).

The title compound was prepared by procedure as described in example I17 (protocol C) starting from 4-Bromo-3-methoxy-benzoic acid. In this particular case, methyltrifluoromethanesulfonate (1.2eq) was added once and the basic aqueous layer was extracted with DCM. The crude was chromatographed on silica gel eluting with cyclohexane containing from 0 to 10% ethylacetate. The oil obtained was triturated in diethylether and the formed white solid was isolated by filtration.

Yield = 26% (overall, the 2 steps).

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.46 (m, 5H), 1.60-1.68 (m, 1H), 1.77-1.88 (m, 4H), 2.58-2.68 (m, 1H), 3.59 (s, 3H), 3.96 (s, 3H), 7.02 (d, 1H), 7.22 (s, 1H), 7.53 (d, 1H)

Example I92.1: R1= cyclohexyl, R2= methyl, R3= 3-methoxy-4-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-2-methoxy-benzamide

I92 was reacted with copper cyanide by the procedure described in example I91-1 and the formed intermediate was transformed to I92.1 following the following protocol:

To a heterogeneous solution of this material (0.9134 mmol, 0.300 g) in ethanol (50 ml), a solution of sodium carbonate (3N) (9.773 mmol, 3.258 ml) and hydrogen peroxide (13.3 ml)

were added and the reaction was heated at 40°C for 1.5 days. The mixture was poured into a saturated solution of $Na_2S_2O_5$ and the solution was concentrated under reduced pressure. The residue was diluted with water, extracted with dichloromethane and the organic layer was washed with water and brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The crude material was purified by chromatography on silica gel eluting with dichloromethane containing from 0 to 4% methanol.

Yield: 25%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.50 (m, 5H), 1.76-1.88 (m, 4H), 2.59-2.69 (m, 1H), 3.60 (s, 3H), 4.02(s, 3H), 5.80-5.90 (b, 1H), 7.25 (d, 1H), 7.34 (s, 1H), 7.62-7.67 (b, 1H), 8.23 (d, 1H).

MS (m/z) / M+1= 347/348

HPLC (uv purity, λ= 214 nm): 97.61%

Example I92.2: R1= cyclohexyl, R2= methyl, R3= 3-hydroxy-4-benzamide

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide

To a mixture of I92.1 and n-tetrabutylammonium iodide (0.433 mmol, 0.160 g) in anhydrous dichloromethane (2 ml) under nitrogen atmosphere at -78°C, a solution of BCl_3 1M in dichloromethane (0.433 mmol, 0433 ml) was added and the reaction mixture was allowed to stir at -78°C for 10 min followed by 2h at 0°C and 1h30 at room temperature. Then, a solution of BCl_3 1N in dichloromethane (0.433 mmol, 0433 ml) was added. After an additionnal 1h30 of stirring at room temperature, the reaction was quenched with water and basified with a saturated solution of sodium bicarbonate before extraction with dicloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane containing from 0 to 4% of methanol to give the desired product.

Yield= 26%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.50 (m, 5H), 1.63-1.70 (m, 1H), 1.80-1.90 (m, 4H), 2.58-2.68 (m, 1H), 3.60 (s, 3H), 5.70-6.20 (b, 2H), 7.18 (s, 1H), 7.24 (d, 1H), 7.38 (d, 1H), 12.25 (s, 1H).

MS (m/z) / M+1= 333/334

HPLC (uv purity, λ= 214 nm): 96.54%

Example I93: R1= cyclohexyl, R2= methyl, R3= 3-nitro-4-methoxycarbonyl-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-2-nitro-benzoic acid methyl ester

I93 was prepared by the procedure described in example I21 (protocol C) using the appropriate intermediates and reagents. In this particular case, triethylamine was not used and the expected product was isolated by filtration after treatment with a saturated solution of $NaHCO_3$.

Yield= 77%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.48 (m, 5H), 1.64-1.70 (m, 1H), 1.80-1.90 (m, 4H), 5.58-5.66 (m, 1H), 3.63 (s, 3H), 3.82 (s, 3H), 7.80-7.84 (m, 2H), 8.11 (s, 1H).

Example I93.1: R1= cyclohexyl, R2= methyl, R3= 3-amino-4-methoxycarbonyl-phenyl

2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

To a solution of I93 (1.328 mmol, 0.500 g) in ethanol (20 ml), tin chloride dihydrate (6.641 mmol, 1.495 g) was added and the mixture was heated at reflux for 5h then allowed t stand at room temperature overnight. The mixture was evaporated to dryness and the crude material was basified with a saturated solution of sodium carbonate before extraction with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vaccum. The residue was chromagraphed on silica gel eluting with dicloromethane containing from 0 to 2% of methanol to afford the desired compound.

Yield: 65%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.49 (m, 5H), 1.60-1.69 (m, 1H), 1.80-1.90 (m, 4H), 2.58-2.67 (m, 1H),3.60 (s, 3H), 3.89(s, 3H), 5.77-5.83 (b, 2H), 7.88-7.92 (m, 2H), 7.89 (d, 1H).

MS (m/z) / M+1= 347/349

HPLC (uv purity, λ= 214 nm): 98.31%

Example I93.2: R1= cyclohexyl, R2= methyl, R3= 3-acetylamino-4-methoxycarbonyl-phenyl

2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

To a suspension of I93.1 (0.144 mmol, 0.05 g) in anhydrous toluene (2 ml) at 0°C, triethylamine (0.150 mmol, 0.015 ml) and acetic anhydride (0.160 mmol, 0.015 ml) were added. The reaction was allowed to stir at room temperature for 3 days and 5.4 more equivalents of acetic anhydride and triethylamine were added. After 2 days of stirring at room temperature the mixture was evaporated to dryness and the residue was chromatographed on silica gel eluting with dichloromethane containing from 0 to 1% of methanol.

Yield = 89%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.49 (m, 5H), 1.60-1.67 (m, 1H), 1.76-1.88 (m, 4H), 2.28 (s, 3H), 2.60-2.70 (m, 1H), 3.60 (s, 3H), 3.93 (s, 3H), 7.45 (d, 1H), 8.03 (d, 1H), 8.98 (s, 1H), 11.10 (s, 1H).

MS (m/z) / M+1= 389/390

HPLC (uv purity, λ=214 nm): 96.93%

Example I93.3: R1= cyclohexyl, R2= methyl, R3= 3-amino-4-benzamide

2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

I93 was modified following the procedure described in example I37.3 to afford the amide derivative with an overall yield 84%. The reduction of the nitro group to give I93.3 was performed as described in example I93.1. In this particular case, the reactionnal mixture was basified with a

saturated solution of sodium carbonate then distilled. The crude was diluted in water and extracted with dicloromethane. The aqueous phase, saturated with brine, was then extracted with ethylacetate and the organic layer was dried over $MgSO_4$, filtered and evaporated to drynsss to give a residue which was purified by two consecutive chromatographies on silica gel, eluting first with dichloromethane/methanol (93/7) and the second purification made eluting with a gradient of cyclohexane containing from 0 to 40% ethylacetate.

Yield= 10%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.27-1.40 (m, 5H), 1.56-1.62 (m, 1H), 1.70-1.80 (m, 4H), 2.58-2.65 (m, 1H), 3.50 (s, 3H), 6.73-6.78 (m, 3H), 7.00 (s, 1H), 7.10-7.20 (b, 1H), 7.61 (d, 1H), 7.75-7.85 (b, 1H).

MS (m/z) / M+1= 332/333

HPLC (uv purity, λ= 214 nm): 95.83%

Example I93.4: R1= cyclohexyl, R2= methyl, R3= 4-oxo-3,4-dihydro-quinazoline-7-yl

7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one

A mixture of I93.1 (1.443 mmol, 0.500 g) and formamide (4 ml) was stirred and heated at reflux for 2h before cooling at room temperature. The mixture was diluted with water and the precipitate was collected by filtration. The precipitate was washed with water and petroleum ether and purified by chromatography on silica gel, eluting with dichloromethane containing from 0 to 3% of methanol followed by an isocratic elution with dichloromethane/methanol (93/7).

Yield= 20%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.55-1.64 (m, 1H), 1.70-1.83 (m, 4H), 2.63-2.71 (m, 1H), 3.56 (s, 3H), 7.73 (s, 1H), 7.00 (s, 1H), 7.80 (d, 1H), 8.12-8.19 (m, 3H), 12.30-12.40 (b, 1H).

MS (m/z) / M+1= 342/343

HPLC (uv purity, λ= 214 nm): 95.19%

Example I93.5: R1= cyclohexyl, R2= methyl, R3= 4-amino-quinazoline-7-yl

7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-quinazolin-4-ylamine

A mixture of I93.4 (0.264 mmol, 0.090 g), thionyl chloride (2 ml) and a catalytic amount of dimethylformamide was refluxed for 2h before distillation of solvents under reduced pressure. To the residue, a solution of NH_3 (0.5N) in dioxan (4 ml) was added and the mixture was heated in a sealed tube at 80°C for 4 days. The mixture was then evaporated to dryness and the crude was diluted in a solution of acetic acid (0.1 ml AcOH in 10 mml H_2O), and extracted with dichloromethane to remove the impurities. The aqueous phase was then basified with a solution NaOH (0.1N) and then extracted with dichloromethane. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the desired product.

Yield= 7.5%.

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.29-1.50 (m, 5H), 1.60-1.69 (m, 1H), 1.79-1.90 (m, 4H), 2.65-2.72 (m, 1H), 3.65 (s, 3H), 5.60-5.70 (b, 2H), 7.75 (d, 1H), 7.90 (s, 1H), 7.98 (d, 1H), 8.67 (s, 1H).

MS (m/z) / M+1= 341/343

HPLC (uv purity, λ= 214 nm): 99.99%

Example I93.6: R1= cyclohexyl, R2= methyl, R3= 2,4-Dioxo-1,2,3,4-tetrahydro-quinazoline-7-yl

7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione

To a solution of I93.3 in THF (4ml), carbonyldiimidaz le (0.464 mmol, 0.080 g) was added and the reaction was heated at reflux overnight. Carbonyldiimidazole (0.464 mmol, 0.080 g) was added and the mixture was kept at reflux for 24h. Then, the solvent was distilled and the residue was purified by chromatography on silica gel, eluting with a gradient of cyclohexane containing from 15 to 30%. The chromatographied

product was solubized in ethylacetate and the rganic layer was washed with water. The collected organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to give the title product.

Yield= 13.3%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.28-1.39 (m, 5H), 1.56-1.64 (m, 1H), 1.72-1.82 (m, 4H), 2.62-2.67 (m, 1H), 3.54 (s, 3H), 7.41-7.43 (m, 2H), 7.94 (d, 1H), 11.17 (s, 1H), 11.36 (s, 1H).

MS (m/z) / M+1 = 358/359

HPLC (uv purity, λ= 214 nm): 96.70%

Example I94: R1= cyclohexyl, R2= methyl, R3= 3-methoxy-4-sulfamoyl-phenyl

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide

The title compound was prepared by the procedure described in example I19 (protocol C) using the appropriate intermediates and reagents. The residue was purified by chromography on silica gel, eluting with dicloromethane containing from 0 to 2% of methanol.

Yield= 59%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.49 (m, 5H), 1.63-1.69 (m, 1H), 1.77-1.87 (m, 4H), 2.59-2.67 (m, 1H), 3.60 (s, 3H), 4.06 (s, 3H), 5.02 (s, 2H), 7.20 (d, 1H), 7.40 (s, 1H), 7.90 (d, 1H).

MS (m/z) / M+1 = 384/386

HPLC (uv purity, λ= 214 nm): 99.99%

Example I95: R1= cyclohexyl, R2= methyl, R3= 4-methoxy-3-sulfamoyl-phenyl

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide

The title compound was prepared by procedure as described in example I18 (protocol C) using the appropriate intermediates and reagents.

In this particular case, the residue obtained after extraction and distillation was triturated with methanol and the precipitate was filtered off and purified by silica gel chromatography, eluting with a mixture of cyclohexane/ethylacetate (1/1).

Yield= 9%.

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.30-1.50 (m, 5H), 1.62-1.70 (m, 1H), 1.80-1.90 (m, 4H), 2.58-2.65 (m, 1H), 3.58 (s, 3H), 4.02 (s, 3H), 5.10 (s, 2H), 7.09 (d, 1H), 7.80 (d, 1H), 8.12 (s, 1H).

MS (m/z) / M+1 = 383/384

HPLC (uv purity, λ= 214 nm): 99.38%

Example I96: R1= 3-methoxycarbonyl-phenyl, R2= methyl, R3= 3-cyano-phenyl

3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester

To a solution of 7j (1.25 mmol, 0.42 g) in anhydrous dioxane (14 mL), was added methyltrifluoromethane sulfonate (1.5 mmol, 142 µl). The resultant mixture was stirred for 24h at room temperature. To this solution was added methyltrifluoromethane sulfonate (0.45 mmol, 43 µl) to ensure completion of the reaction. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with an aqueous saturated solution of $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude material was purified by 2 sucessive flash chromatographies (eluent: dichloromethane/methanol 95/5 and cyclohexane/ethyl acetate 90/10) to give the desired compound 0.23 g (yield 53%).

^{1}H-NMR (400 MHz , DMSO) δ ppm: 3.75 (s, 3H), 3.86 (s, 3H), 7.34(d, 1H), 7.54 (t, 1H), 7.61 (s, 1H), 7.67-7.70 (m, 2H), 7.94 (d, 1H), 8.02 (d, 1H), 8.12(s, 1H).

MS (m/z) / M+1: 351/353

Example I96.1: R1= 3-benzoic-acid, R2= methyl, R3= 3-cyano-phenyl

3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

A mixture of I96 (3 mg, 8.56 mmol) and potassium hydroxyde (1N in water, 12.8 mmol, 12.8mL) in tetrahydrofuran (90 ml) was stirred at room temperature overnight. The reaction mixture was heated at reflux for 1h. After cooling, the reaction mixture is concentrated, water is added (2 mL) and a solution of HCl (1N in water, 12.8 mmol, 12.8 mL) is added. The precipitate is collected by filtration and washed succesively with water and with ether before being dried under vacuum at 45°C. The compound was purified by flash chromatography (eluent: dichloromethane/methanol 99/1 +1% acetic acid) to give 2.38 g of the title product

Yield: 83%

^{1}H-NMR (400 MHz , DMSO) δ ppm : 3.8 (s, 3H), 7.31 (d, 1H), 7.51 (t, 1H), 7.61 (s, 1H), 7.65-7.69 (m, 2H), 7.93 (d, 1H), 8.01 (d, 1H), 8.11 (s, 1H), 13.06 (s, 1H).

MS (m/z) / M+1 = 337/338

HPLC (uv purity, λ= 245 nm): 99.6%

Example I97: R1= 3-methoxycarbonyl-phenyl, R2= methyl, R3= 2-pyridyl

3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester

To a solution of 7k (1.76 mmol, 0.55 g) in anhydrous dioxane (14 mL) and triethylamine (1.76 mmol, 264 µL), methyltrifluoromethane sulfonate (1.76 mmol, 199 µL) was added. The resultant mixture was stirred for 24h. To this solution was added methyltrifluoromethane sulfonate (0.53 mmol, 60 µL) and triethylamine (0.53 mmol, 79.2 µL) to allow reaction to completion. The solvent was removed by distillation under reduced pressure to give a crude material which was basified with an aqueous saturated solution of $NaHCO_3$ and extracted with dichl romethane. The rganic layer was dried over Na_2SO_4, filtered and concentrated. The crude

material was purified by filtration on silica gel (eluent: dichloromethane) to give the desired compound.

Yield: 28%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3.76 (s, 3H), 3.86 (s, 3H), 7.35 (dd, 1H), 7.48-7.54 (m, 2H), 7.64-7.68 (m, 2H), 7.96-8.00 (m, 2H), 8.58 (d, 1H).

MS (m/z) / M+1: 327/329

Example I97.1: R1 =3-benzoic-acid, R2= methyl, R3= 2-pyridyl

3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

A mixture of I97 (16 g,0.49 mmol) and potassium hydroxyde (1N in water, 0.58 mmol, 0.58 mL) in tetrahydrofuran (3ml) was stirred at room temperature for 48h. The reaction mixture was heated at reflux for 2h. After cooling, the reaction mixture is concentrated, water is added (5 mL), the aqueous layer was extrated with dichloromethane and neutralized with a solution of HCl (0.1N in water). The precipitate is collected by filtration and washed successively with water and with ether before being dried under vacuum at 45°C to give 0.08 g of the title product.

Yield: 54%

^{1}H-NMR (400 MHz , DMSO) δ ppm: 3.8 (s, 3H), 7.31 (d, 1H), 7.47-7.49(m, 2H), 7.64-7.66 (m, 2H), 7.96-7.98 (m, 2H), 8.58 (d, 1H)

MS (m/z) / M+1= 313/314/315

HPLC (uv purity, λ= 245 nm): 97.6%

Example I98: R1= 3-benzoic-acid, R2= methyl, R3= 4-Chloro-3-sulfamoyl-phenyl

3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid

I98 was prepared by the procedure described in example I96.1 using the appropriate intermediates and reagents. In this particular case, the ester intermediate was basified with triehylamine. The title product was isolated by

chromatography on silica gel, eluting with ethylacetate / cyclohexane (15/85).
Yield=19% (2 steps)
^{1}H-NMR (400MHz, DMSO) δ ppm: 3.73 (s, 3H), 3.85 (s, 3H), 7.35 (d, 1H), 7.54 (t, 1H), 7.62 (s, 1H), 7.70 -7.80 (m, 4H), 7.86 (d, 1H), 8.24 (s, 1H).
MS (m/z) / M+1 = 439/441

Then, A solution (1N) of potassium hydroxide (1.139mmol, 1.14ml) was added to a solution of the ester derivative (0.456mmol, 0.2g) in THF (5ml) and the mixture was stirred overnight. The reaction mixture was evaporated to dryness and the residue was diluted in ethanol and acidified with a solution (6.9N) of HCl in ethanol (0.165ml). The mixture was stirred at RT for 5h and the solvent was distilled under reduced pressure. The crude material was chromatographed on silica gel, eluting with a gradient of dichloromethane containing from 5 to 25% methanol. The isolated product was solubilized in THF and filtered through a pad of silica gel and the filtrate was evaporated to dryness to afford the desired product.
Yield = 37%.
^{1}H-NMR (400MHz, CDCl3) δ ppm: 3.74 (s, 3H), 7.24 (d, 1H), 7.45 (t, 1H), 7.62 (s, 1H), 7.66 (d, 1H), 7.73-7.80 (m, 3H), 7.84 (d, 1H), 8.23 (s, 1H).
MS (m/z) / M+1= 425/427
HPLC (uv purity, λ= 214 nm): 94.86%

EXAMPLE I: PROTOCOL D

Example I99: R1= cyclohexyl, R2= methyl, R3= 4-cyano-phenyl 4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile

Compound I99 was prepared by the procedure described in exemple I15 (protocol D).

To a mixture of 4-cyanobenzoic acid (74.8 mmol, 11 g), 2-methylthiosemicarbazide 5a (74.8 mmol, 13.42 g) in anhydrous dioxane (110 mL) at 70°C, $POCl_3$ (89.65 mmol, 76.76 ml) was added and the mixture was warmed at 95°C for 4 hours. The solvent was removed by distillation under reduced pressure to give a crude material which was basified at pH 8-7 with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with dichoromethane. The organic layer was washed with water and saturated solution of NaCl, dried over magnesium sulfate, filtered and distilled to give a residue which was purified by silica gel chromatography (eluted with a gradient of cyclohexane/ethyl acetate finishing with the ratio 90/10) to afford 8.5 g of the title compound.
Yield: 42%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.15-1.40 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.83 (m, 4H), 2.57-2.70 (m, 1H), 3.55 (s, 3H), 7.82 (dd, 2H), 7.93 (dd, 2H).

Example I99.1: R1= cyclohexyl, R2= methyl, R3= 4-(1H-tetrazol-5-yl)-phenyl
Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine
To a solution of I99 (1.67 mmol, 500 mg) in toluene (2 ml), sodium azide (2.18 mmol, 142 mg), triethylamine hydrochloride (2.18 mmol, 300 mg) were added and the mixture was warmed at reflux during 24 hours. The reaction mixture was cooled at room temperature, acidified with a solution f HCl [0.1N], and then basified at pH=6-7 with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with ethyl acetate and the organic layer was washed with a saturated solution of NaCl, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel column using a gradient of dichloromethane containing from 0 to 20% methanol to afford the title compound.
Yield: 61%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.42 (m, 5H), 1.55-1.65 (m, 1H), 1.70-1.85 (m, 4H), 2.60-2.72 (m, 1H), 3.55 (s, 3H), 7.85 (dd, 2H), 8.13 (dd, 2H)
MS (m/z) / M+1= 341/342
HPLC (uv purity, λ = 214 nm)= 99.9%

Example I100: R1= cyclohexyl, R2= methyl, R3= 4-nitro-phenyl
Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4] thiadiazol-2-ylidene]-amine

I100 was prepared as described in example I15 (protocol D) using the appropriate reagents. The crude material was purified by silica gel chromatography eluting with a gradient of cyclohexane containing from 0 to 10% ethylacetate.
Yield: 40%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.20-1.40 (m, 5H), 1.57-1.64 (m, 1H), 1.72-1.83 (m, 4H), 2.61-2.91 (m, 1H), 3.56 (s, 3H), 7.89 (d, 2H), 8.29 (d, 2H).
MS (m/z) / M+1 = 319/320

Example I100.1: R1= cyclohexyl, R2= methyl, R3= 4-amino-phenyl
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine

Tin chloride dihydrate (93.278 mmol, 20.987 g) was added to a solution I100 (18.656 mmol, 5.940 g) in ethanol at 70°C and the mixture was refluxed for 1h30. The mixture was then filtered on Celite and the filtrate was evaporated to dryness. The crude material was basified with a saturated solution of sodium bicarbonate then extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The residue was filtred through a pad of silica gel with a mixture of dichloromethane/methanol (95/5).
Yield= 62%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.19-1.37 (m, 5H), 1.56-1.63 (m, 1H), 1.70-1.80 (b, 4H), 2.56-2.74 (m, 1H), 3.44 (s, 3H), 5.60 (s, 2H), 6.58 (d, 2H), 7.29 (d, 2H).
MS (m/z) / M+1= 289/290
HPLC (uv purity, λ= 214 nm): 97.61%

Example I100.2: R1= cyclohexyl, R2= methyl, R3= 4-(N-cyano-N'-(2-dimethylaminoethyl)carboximidamide)-phenyl
[5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of diphenylcyanocarbonimidate (0.364 mmol, 0.087 mmol) in acetonitrile (1 ml) at 70°C, I100.1 (0.347 mmol, 0.1 g) was added and the reaction mixture was heated at 80°C for 15h. 1eq. of carbonimidiate was added and the mixture was kept at 80°C for an additional 5h before evaporation of volatiles. The residue was mixed with ethanol (2 ml) and N,N-dimethylethylene diamine (0.34 mmol, 0.038 mg). The mixture was stirred at room temperature for 15h and heated at reflux for 5h. On cooling to room temperature, the precipitate formed was filtered off and purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 2 to 5% methanol.
Yield= 32%
^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.16-1.41 (m, 5H), 1.50-1.70 (m, 1H), 1.80-1.91 (m, 4H), 2.35 (s, 6H), 2.50-2.60 (m, 3H), 3.31-3.38 (m, 2H), 3.55 (s, 3H), 6.00-6.10 (b, 1H), 7.30 (d, 2H), 7.52 (d, 2H).
MS (m/z) / M+1 = 427/428
HPLC (uv purity, λ= 214 nm): 97.23%

Example I100.3: R1= cyclohexyl, R2= methyl, R3= 4-acetamide-phenyl
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide

To a solution of I100.1 (0.347 mmol,0.1 g) in presence of triethylamine (0.361 mmol, 0.051 ml) in anhydrous toluene (3

ml) at 0°C, acetic anhydride (0.382 mmol, 0.036 ml) was added and the reaction mixture was stirred at room temperature for 20h and then concentrated to dryness. The residue was mixed with a saturated solution of sodium bicarbonate and then the aqueous mixture was extracted with dichloromethane. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel chromatography eluting with a mixture of methanol/dichloromethane (2/98).
Yield=22%.

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.22-1.45 (m, 5H), 1.58-1.68 (m, 1H), 1.80-1.88 (m, 4H), 2.21 (s, 3H), 2.58-2.64 (m, 1H), 3.60 (3H, s),7.20 (s, 1H), 7.52-7.62 (m, 4H).
MS (m/z) / M+1 = 331:332
HPLC (uv purity, λ= 214 nm): 95.24%

Example I100.4: R1= cyclohexyl, R2= methyl, R3= 4-(bis-ethylsulfonyl-amino)-phenyl
[5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of I100.1 (0.347 mmol, 0.1 g) in dichloromethane (5 ml) with triethylamine (0.520 mmol, 0.072 ml), chlorosulfonyl chloride (0.590 mmol, 0.057 ml) was added at 0°C and the mixture was stirred at room temperature for 4h30 before evaporation to dryness under reduced pressure. The crude material was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 5% methanol.
Yield= 76%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.52 (m, 11H), 1.61-1.68 (m, 1H), 1.80-1.89 (m, 4H), 2.59-2.68 (m, 1H), 3.58-3.64 (m, 7H),7.40 (d, 2H), 7.70 (d, 2H).
MS (m/z) / M+1= 473/475
HPLC (uv purity, λ= 214 nm): 98.68%

Example I100.5: R1= cyclohexyl, R2= methyl, R3= 4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl

[5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine

To a solution of 1,1-bis(methylthio)-2-nitroethylene (1.041 mmol, 0.172 g) in acetonitrile (1 ml), at 75°C, I100.1 (0.347 mmol, 0.1 g) was added and the reaction was heated at reflux for 7h. The reaction mixture was then evaporated to dryness and the crude material was purified by silica gel chromatography eluting with a gradient of dichloromethane containing from 0 to 5% of methanol to give the desired intermediate (0.09 g, yield: 64%).

A mixture of ethylenediamine (0.133 mmol, 0.017 ml) and this intermediate (0.111 mmol, 0.045 g) in ethanol (2 ml) was heated at reflux for 3h. The mixture was concentrated under reduce pressure to give a residue which was purified by silica gel chromatography eluting with dichloromethane containing 2% methanol.

Yield= 90%

^{1}H-NMR (400MHz,$CDCl_3$) δ ppm: 1.23-1.49 (m, 5H), 1.65-1.70 (m, 1H), 1.78-1.88 (m, 4H), 2.45 (s, 6H), 2.57-2.71 (m, 3H), 3.51-3.61 (m, 5H), 6.66 (s, 1H), 7.09 (d, 2H), 7.60 (d, 2H), 10.55-10.62 (b, 1H), 12.28-12.40 (b, 1H).

MS (m/z) / M+1= 446/447

HPLC (uv purity, λ= 214 nm): 99.34%

Example I100.6: R1= cyclohexyl, R2= methyl, R3= 4-(1-amino-2-nitro-vinylamino)-phenyl

(E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine

The title product was prepared by the procedure described in example I100.5 using a solution of ammonia (2N) in methanol (80 eq) instead of ethylenediamine.

The desired product was isolated by chromatography on silica gel, eluting with a gradient of dichloromethane containing from 2 to 4 % methanol.

Yield= 83%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.47 (m, 5H), 1.62-1.67 (m, 1H), 1.76-1.87 (m, 4H), 2.60-2.66 (m, 1H), 3.60 (m, 3H), 6.70 (s, 1H), 7.24 (d, 2H), 7.67 (d, 2H).
MS (m/z) / M+1 = 375/376
HPLC (uv purity, λ= 214 nm): 94.09%

Example I100.7: R1= cyclohexyl, R2= methyl, R3= 4-(*N*-cyano-*N'*-methyl-carboximidamide)-phenyl
[5-(*N*-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine
To a solution of diphenylcyanocarbonimidate (0.364 mmol, 0.087 g) in acetonitrile (1 ml) at 70°C, I100-1 (0.347 mmol, 0.1 g) was added and the mixture was heated at 80°C for 15h. One equivalent of diphenylcyanocarbonimidate was added and the mixture was stirred for 5h. The mixture was concentrated under reduced pressure to give the intermediate which was used without further purification. The intermediate (0.416 mmol, 0.300 g) in a solution (2N) of methylamine in MeoH (32.890 mmol, 16.64 ml) was refluxed for 8h then allowed t stand at room temperature for 2 days. The mixture was evaporated to dryness and the residue was purified by chromatography on silica gel, eluting with a gradient of dichloromethane containing from 0 to 4% of methanol to give the desired product.
Yield: 29%
^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.45 (m, 5H), 1.62-1.67 (m, 1H), 1.76-1.87 (m, 4H), 2.57-2.67 (m, 1H), 2.90 (d, 3H), 3.60 (m, 3H), 4.90-5.01 (b, 1H), 7.17-7.28 (m, 3H), 7.69 (d, 2H).
MS (m/z) / M+1= 370/371
HPLC (uv purity, λ= 214 nm): 99.99%

Example I100.8: R1= cyclohexyl, R2= methyl, R3= 4-(N-cyano-N'-amino-carboximidamide)-phenyl
[5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiaz 1-2-ylidene]-cyclohexyl-amine

The title product was prepared by the procedure described in example I100.7 using the same intermediate (0.416 mmol, 0.300 g) and a solution (2N) of ammonia in methanol (32.89 mmol, 16.64 ml). The desired product was purified by chromatography on silica gel eluting with a gradient f dichloromethane containing from 0 to 7% methanol.

Yield= 67%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.46 (m, 5H), 1.60-1.66 (m, 1H), 1.78-1.88 (m, 4H), 2.55-2.65 (m, 1H), 3.58 (m, 3H), 6.10 (s, 2H), 7.42 (d, 2H), 7.55 (d, 2H), 8.71 (s, 1H).

MS (m/z) / M+1 = 356/357

HPLC (uv purity, λ= 214 nm): 97.39%

Example I100.9: R1= cyclohexyl, R2= methyl, R3= 4-ethylsulfonylamino-phenyl

Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide

Ethylsulfonyl chloride (0.416 mmol, 0.040 ml) was added t a solution of I100.1 (0.347 mmol, 0.10 g) in dichloromethane at 0°C. The mixture was stirred for 12 h at room temperature then basified with a saturated solution of sodium bicarbonate. The organic layer was collected and concentrated under reduce pressure. The crude material was reacted with 1,1-bis(methylthio)-2-nitroethlene (2.690 mmol, 0.445 g ,10 eq) at reflux in acetonitrile (5 ml) for 24 h. The solvent was then distillated under reduced pressure and the residue was purified by silica gel chromatography eluting with dichloromethane containing a gradient from 0 t 10% methanol.

Yield= 15%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.24-1.44 (m, 8H), 1.62-1.68 (m, 1H), 1.78-1.87 (m, 4H), 2.59-2.65 (m, 1H), 3.14-3.19 (q, 2H), 3.60 (s, 3H); 6.44 (s, 2H), 7.23 (dd, 2H), 7.61 (dd, 2H).

MS (m/z) / M+1= 381/383

HPLC (uv purity, λ= 214 nm): 99.22%

Example I100.10: R1= cyclohexyl, R2= methyl, R3= 4-Ureido-phenyl

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4] thiadiazol-2-yl)-phenyl]-urea

To a solution of I100.1 (0.348 mmol, 0.100 g) in THF (1 ml), trimethylsilyl isocyanate (0.416 mmol, 0.488 ml) was added and the mixture was stirred at room temperature for 10 h and water was added. The organic layer was extracted with ethylacetate, washed with water, brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The crude product was purified by chromatography on silica gel, eluting with a gradient of dichloromethane containing from 0 to 4% of methanol.

Yield= 13%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1.24-1.39 (m, 5H), 1.53-1.57 (m, 1H), 1.69-1.80 (m, 4H), 2.57-2.65 (m, 1H), 3.47 (s, 3H), 5.92 (s, 2H), 7.50 (s, 4H), 8.79 (s, 1H).

MS (m/z) / M+1= 332/333

HPLC (uv purity, λ= 214 nm): 92.50%

Example I100.11: R1= cyclohexyl, R2= methyl, R3= 4-[3-(2-dimethylamino-ethyl)-ureido]-phenyl

1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea

To a solution of I100.1 (0.347 mmol, 0.100 g) with triethylamine (1.041 mmol, 0.145 ml) in dichloromethane anhydrous (5 ml), was added a solution of phosgene (20% in toluene) (1.024 mmol, 0.487 ml) at 0°C. The mixture was stirred at 0°C for 10 min then allowed to raise to room temperature for 1h and N,N-dimethyl-ethylene diamine (0.694 mmol, 0.076 ml) was added. After 20 h of stirring at room temperature, the mixture was basified with a saturated solution of sodium bicarbonate then extracted with dichloromethane. The organic phase was washed with water, brine , dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel

eluting with a mixture dichloromethane/methanol (95/5) t afford the tittle product.

Yield= 11%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.50 (m, 5H), 1.70-1.75 (m, 1H), 1.78-1.90 (m, 4H), 2.33 (s, 6H), 2.58-2.68 (m, 3H), 3.30-3.40 (b, 2H), 3.60 (s, 3H), 5.37-5.47 (b, 1H), 7.40 (d, 2H), 7.55 (d, 2H).

MS (m/z) / M+1 = 403/404

HPLC (uv purity, λ= 214 nm): 99.99%

Example I101: R1= cyclohexyl, R2= methyl, R3= 3-chloro-4-sulfamoyl-phenyl

2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

The title compound was prepared by the procedure described in example I15 (protocol D) using the appropriate intermediates and reagents.

The desired product was isolated by chromatography on silica gel, eluting with a gradient of cyclohexane containing from 0 to 30% ethylacetate.

Yield: 23%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.49 (m, 5H), 1.60-1.69 (m, 1H), 1.79-1.87 (m, 4H), 2.59-2.69 (m, 1H), 3.60 (m, 3H), 5.10 (s, 2H), 7.58 (d, 1H), 7.80 (s, 1H), 8.10 (d, 1H).

MS (m/z) / M+1 = 388/389

HPLC (uv purity, λ= 214 nm): 98.32%

Example I102: R1=cyclohexyl, R2= methyl, R3= 3-chloro-4-methoxycarbonyl-phenyl

2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester

I102 was prepared by procedure as described in example I15 (protocol D) using the appropriate intermediates and reagents. The desired product was isolated by chromatography on silica gel eluting with a gradient of cyclohexane containing from 0 t 7% ethylacetate. (yield : 12%)

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.21-1.48 (m, 5H), 1.60-1.67 (m, 1H), 1.78-1.87 (m, 4H), 2.58-2.66 (m, 1H), 3.60 (s, 3H), 4.93 (s, 3H), 7.55 (d, 1H), 7.71 (s, 1H), 7.86 (d, 1H).

Example I102.1: R1= cyclohexyl, R2= methyl, R3= 3-chloro-4-benzamide

2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

To a solution of I102 (0.391 mmol, 0.147 g) in a mixture of THF/ MeOH (2 ml) (1/1), Lithium hydroxyde (0.430 mmol, 0.010 g) was added and the raction mixture was allowed to stir f r 15h at room temperature. Lithium hydroxyde (0.430 mmol, 0.010 g) was added and the reaction was stirred for 24 h before evaporation to dryness. The crude material was acidified with a solution of HCl (1N), stirred at room temperature for 3h and the mixture was then concentrated to dryness.

Toluene (5 ml) was added to the residue (0.273 mmol, 0.120 g) followed by an addition of thionyl chloride (0.820 mmol, 0.598 ml) and the mixture was heated at reflux overnight before distillation of volatiles under reduced pressure. The residue was poured into THF (5 ml) and cooled to 0°C then a solution of concentrated ammonia (6.833 mmol, 0.448 ml) was added. The reaction was allowed to stir at room temprature for 3 h and then the solvent was distilled. The residue was purified by chromatography on silica gel, eluting with dicloromethane containing from 0 to 1% methanol.

Yield: 63% (overall)

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.48 (m, 5H), 1.62-1.69 (m, 1H), 1.79-1.88 (b, 4H), 2.58-2.67 (m, 1H), 3.60 (m, 3H), 5.86-5.93 (b, 1H), 6.38-6.48 (b, 1H), 7.57 (d, 1H), 7.70 (s, 1H), 7.87 (d, 1H).

MS (m/z) / M+1= 351/353

HPLC (uv purity, λ= 214 nm): 96.60%

Example I103: R1= cyclohexyl, R2= methyl, R3= 4-chloro-3-benzamide

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide

The title compound was prepared by the procedure described in example I102.1 using the appropriate intermediates and reagents (protocol D).

Yield: 47%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1.20-1.42 (m, 5H), 1.60-1.69 (m, 1H), 1.77-1.89 (b, 4H), 2.55-2.65 (m, 1H), 3.60 (m, 3H), 5.89-6.00 (b, 1H), 6.30-6.40 (b, 1H), 7.46 (d, 1H), 7.68 (d, 1H), 8.00 (s, 1H).

MS (m/z) / M+1 = 351/353

HPLC (uv purity, λ= 214 nm): 98.70%

PROTOCOL E: Intermediate 8

R1= cyclohexyl, R2= methyl, R3= 4-methoxycarbonyl-phenyl

1-(4-methoxycarbonyl-benzoyl)-2-methyl-4-cyclohexyl-thiosemicarbazide

To a stirred solution of 5a (2.517 mmol, 0.456 g) in pyridine (6ml), methyl-4-chloro carbonyl benzoate (2.517mmol, 0.500g) was added. The mixture was stirred 24h at RT, and then the pyridine was distilled under reduced pressure. The residue was poured into water and extracted with dichloromethane. The organic layer was washed with water, brine, dried over MgSO4 and concentrated to dryness to afford 1.10g of product.

1H-NMR (400MHz, DMSO) δ ppm: 1.15-1.25 (m, 5H), 1.51-1.61 (m, 1H), 1.61-1.71 (m, 2H), 1.71-1.87 (m, 2H), 3.28 (s, 3H), 3.9 (s, 3H), 4.10-4.21 (m, 1H), 8.00-8.10 (m, 4H), 8.59 (d, 1H), 10.79 (s, 1H).

EXAMPLE I : PROTOCOL E

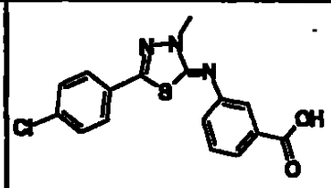
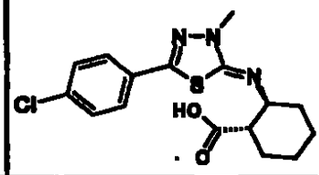
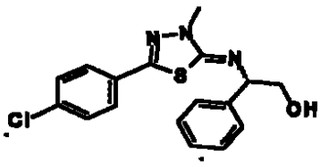
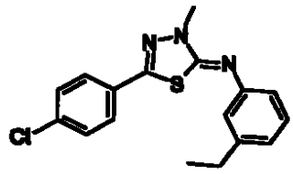
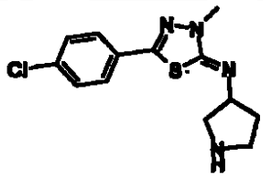
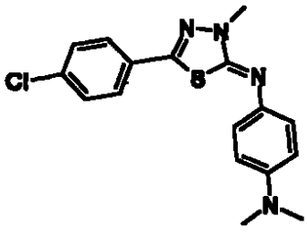
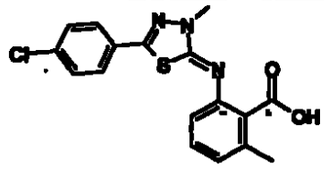
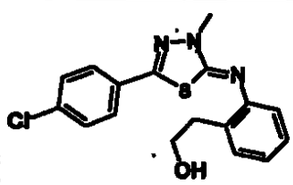
Example I104: R1= cyclohexyl, R2= methyl, R3= 4-methoxycarbonyl-phenyl

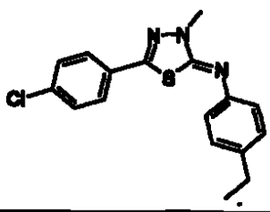
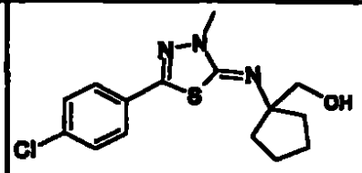
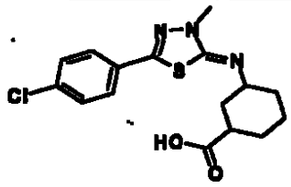
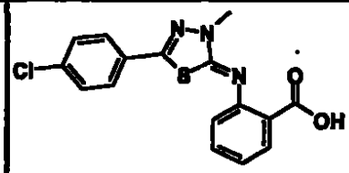
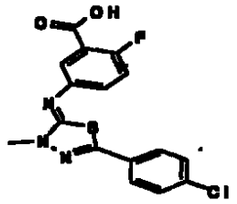
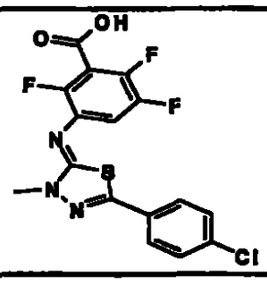
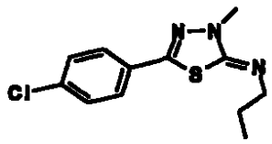
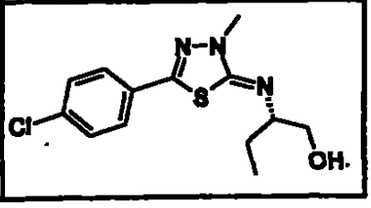
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester

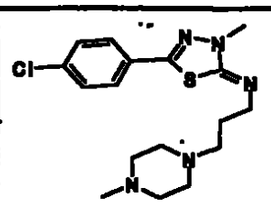
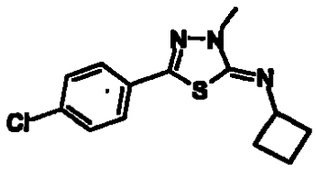
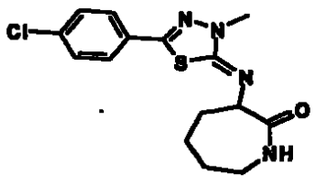
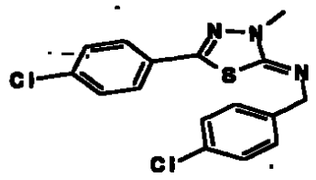
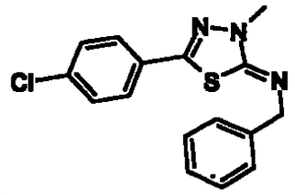
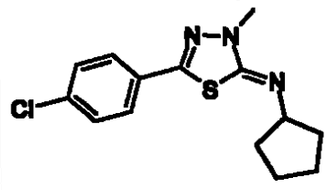
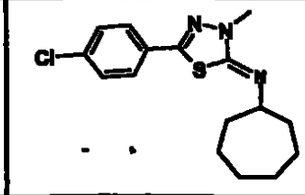
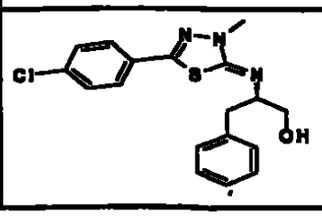
A stirred mixture of the previous intermediate 8 (2.517 mmol, 1.10 g) and methanol (50 ml) was warmed until a homogeneous solution was obtained then mercury oxide (10.068 mmol, 2.18 g) was added. After 18h at reflux, 3 more equivalents of HgO were added and the reaction was kept at reflux for an additionnal 6h then allowed to cool down to RT. The reaction was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure . The crude material was purified by chromatography on silica gel eluting with cyclohexane containing from 10 to 20% ethylacetate.
Yield= 44%.
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.1-1.4 (m, 5H), 1.53-1.61 (m, 1H), 1.69-1.80 (m, 1H), 3.30 (s, 3H), 3.40-3.48 (m, 1H), 3.88 (s, 3H), 3.85 (d, 2H), 7.96 (d, 2H), 8.08 (d, 2H).
MS (m/z) / M+1 =316/318

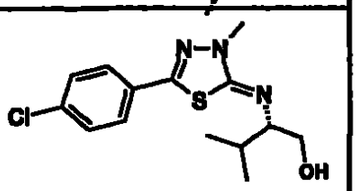
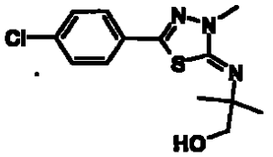
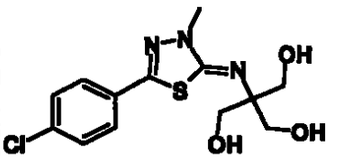
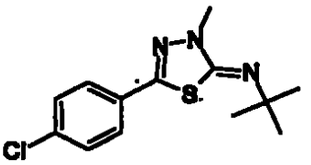
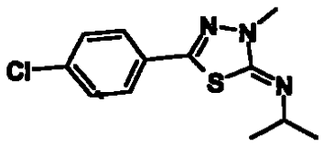
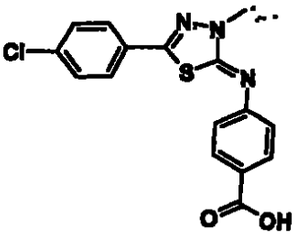
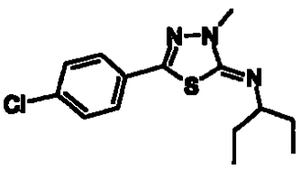
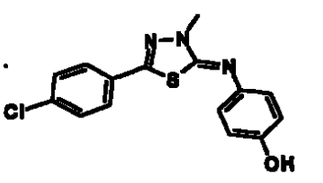
Example 104.1: R1= cyclohexyl, R2= methyl, R3= 4-benzamide
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide
The title compound was prepared by procedure described in example I37.3. The desired product was isolated by chromatography on silica gel eluting with dichloromethane containing from 1 to 2 % methanol.
Yield= 26 % (overall)
^{1}H-NMR (400MHz, DMSO) δ ppm: 1.17-1.40 (m, 5H), 1.58-1.64 (m, 1H), 1.70-1.80 (m, 4H), 3.30 (s, 3H), 3.41-3.51 (m, 1H), 7.50-7.55 (b, 1H), 7.80 (d, 2H), 8.00 (d, 2H), 8.10-8.18 (b, 1H).
MS (m/z) / M+1 =301/302
HPLC (uv purity, λ= 214 nm) = 99.9%

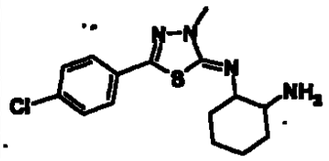
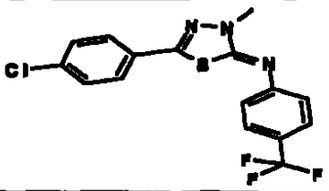
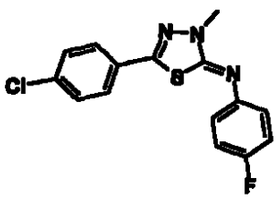
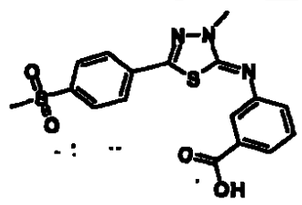
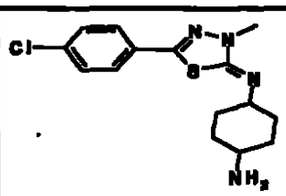
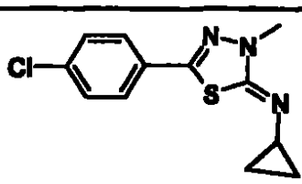
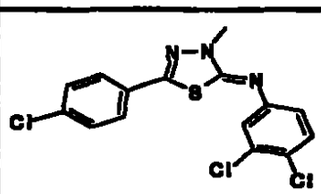
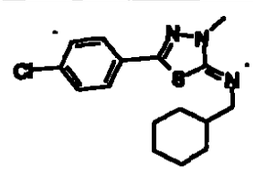
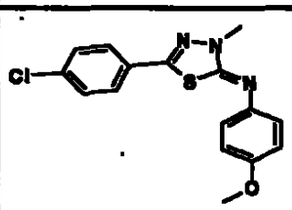
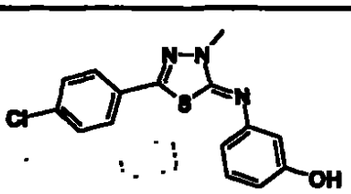
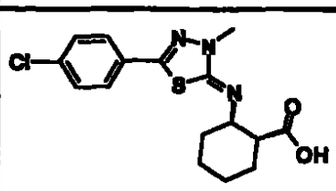
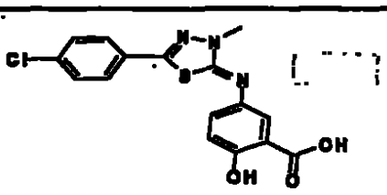
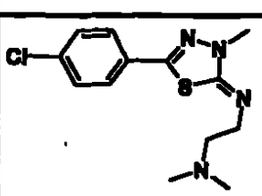
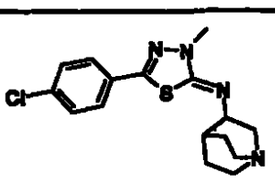
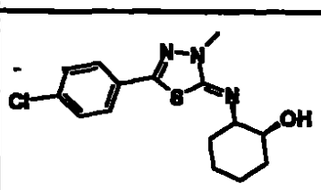
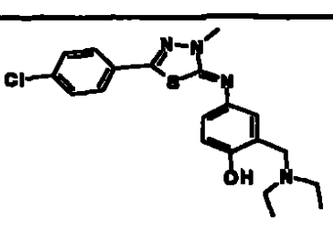
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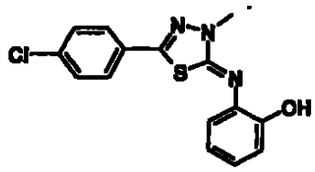
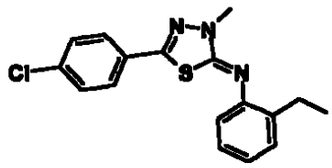
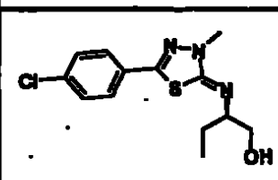
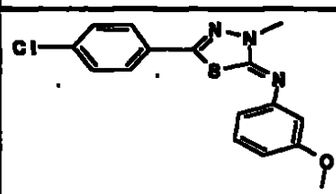
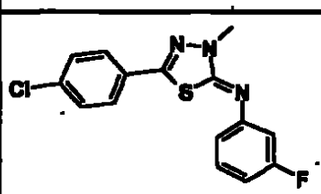
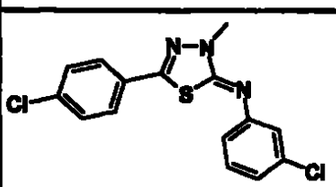
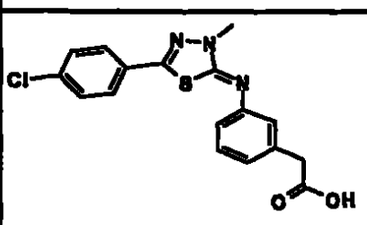
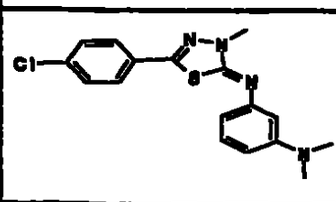
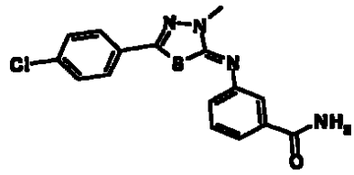
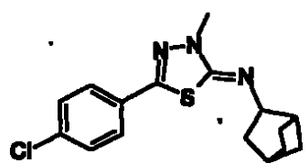
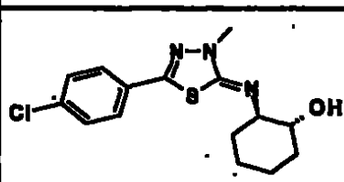
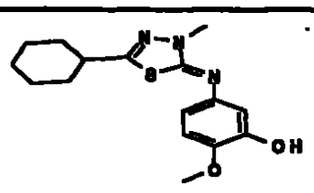
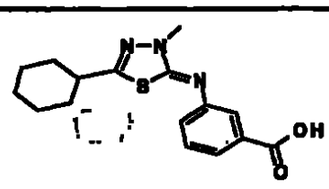
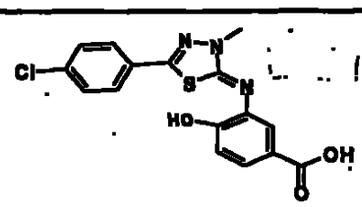
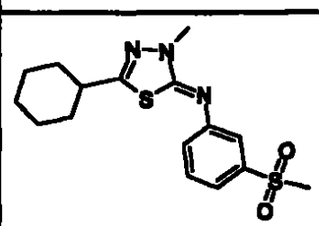
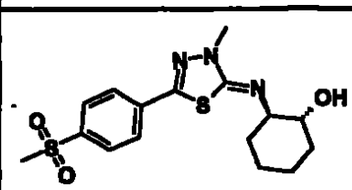
Example	Structure
I1	
I1,1	
I1,2	
I1,3	
I1,4	
I1,5	
I1,6	
I1,7	

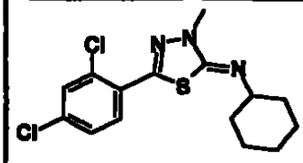
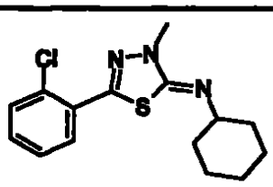
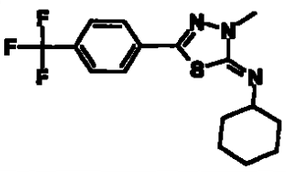
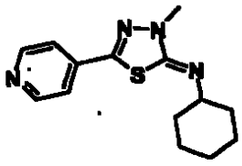
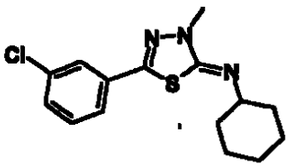
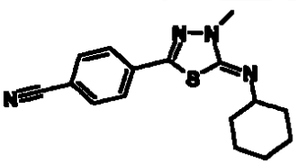
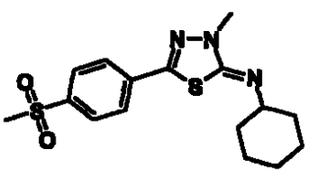
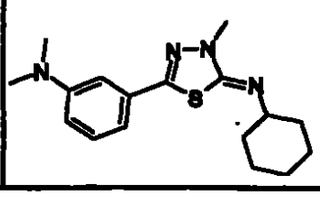
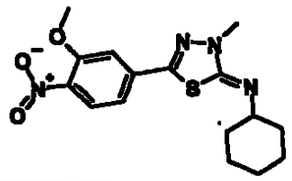
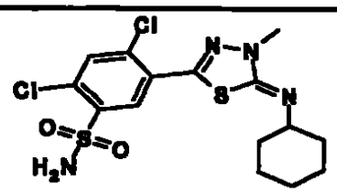
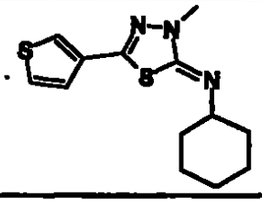
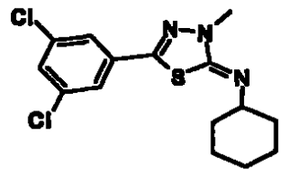
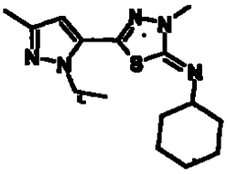
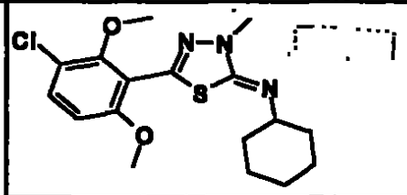
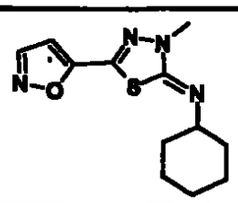
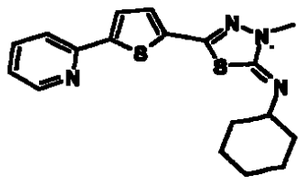
Example	Structure
I1,8	
I1,9	
I1,10	
I2	
I2,1	
I2,2	
I3	
I3,1	

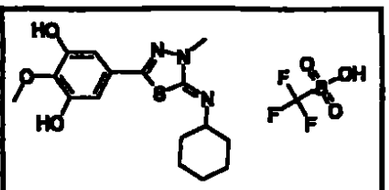
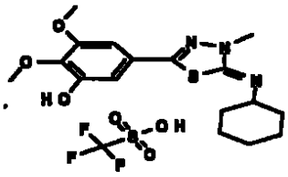
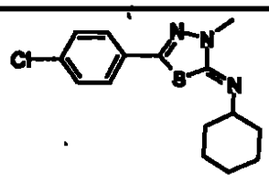
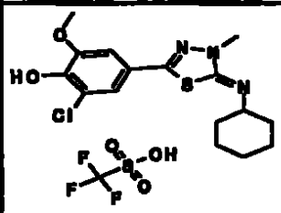
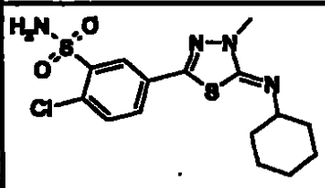
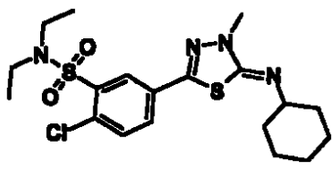
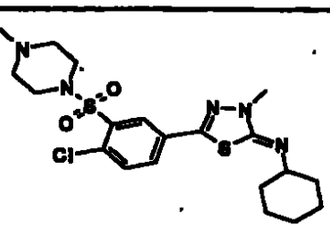
Example	Structure
I3,2	
I3,3	
I3,4	
I3,5	
I3,6	
I3,7	
I3,8	
I3,9	

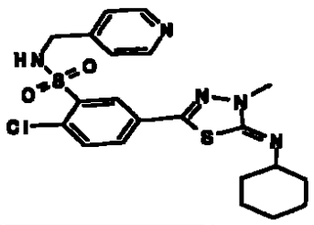
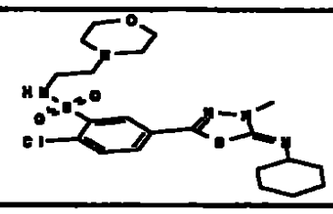
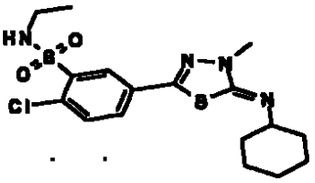
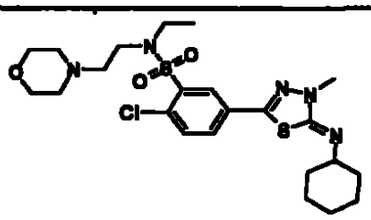
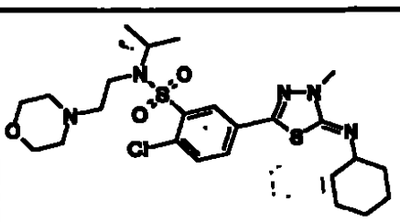
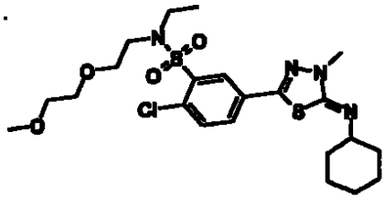
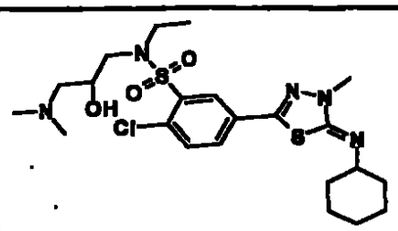
Example	Structure
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I3,11	
I3,12	
I3,13	
I3,14	
I3,15	
I3,16	
I3,17	

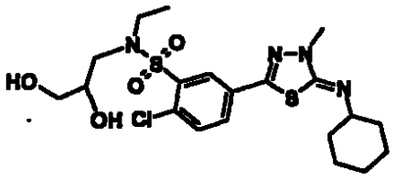
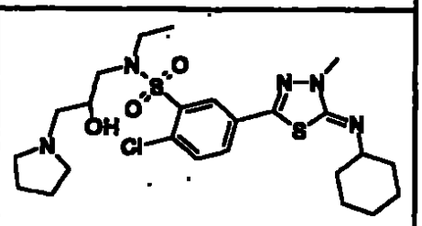
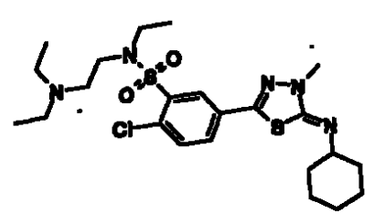
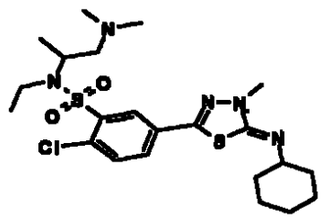
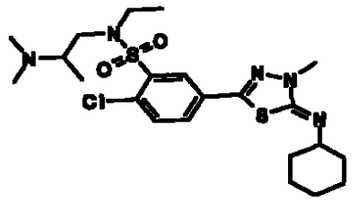
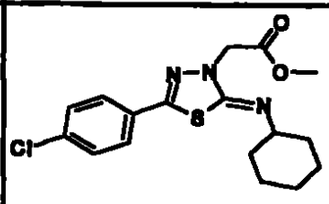
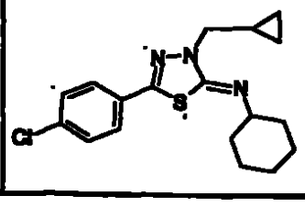
Example	Structure	Example	Structure
I3,18		I3,26	
I3,19		I4	
I3,20		I4,1	
I3,21		I4,2	
I3,22		I5	
I3,23		I6	
I3,24		I6,1	
I3,25		I6,2	

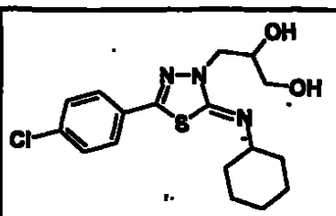
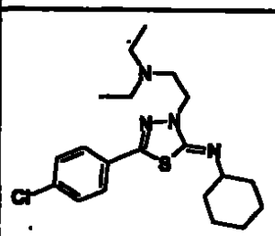
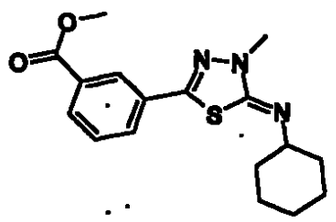
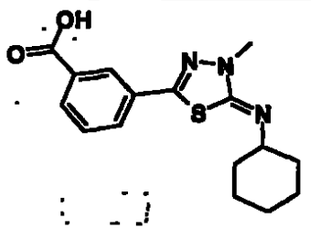
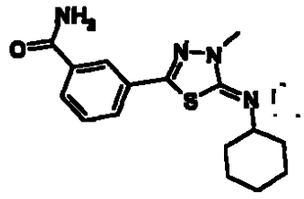
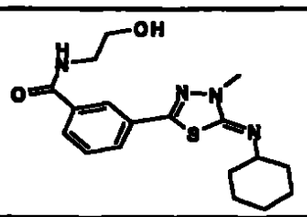
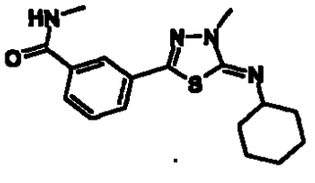
I6,3	
I6,4	
I6,5	
I6,6	
I6,7	
I6,8	
I6,9	
I6,10	
I6,11	
I7	
I8	
I8,1	
I8,2	
I8,3	
I8,4	
I9	

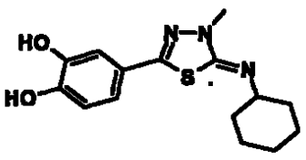
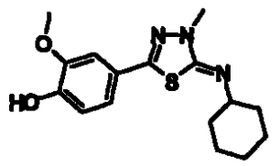
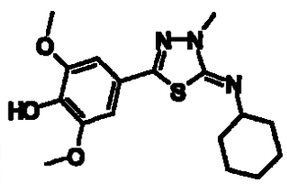
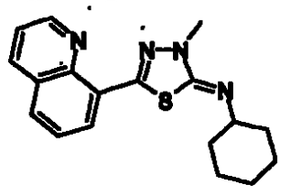
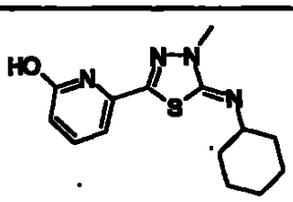
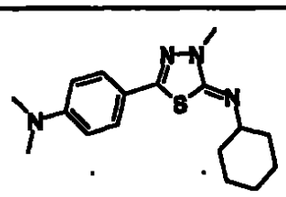
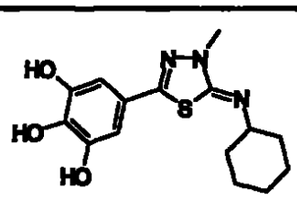
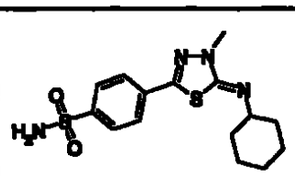
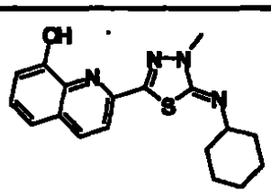
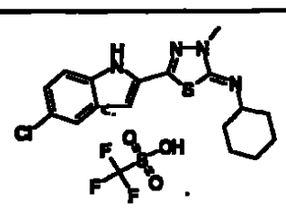
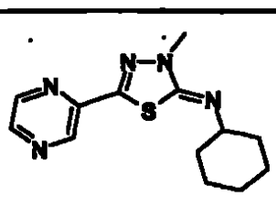
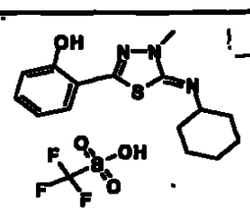
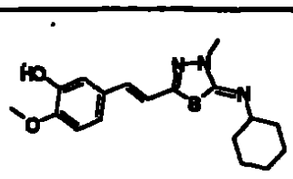
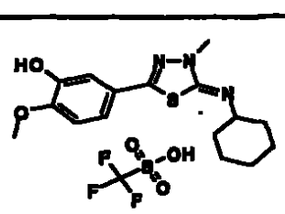
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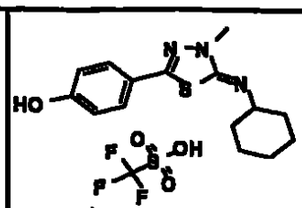
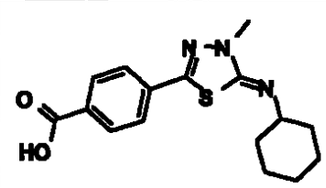
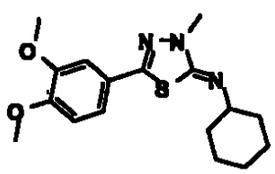
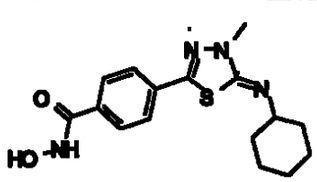
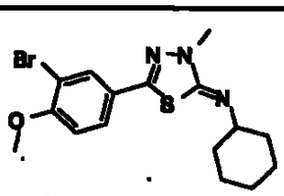
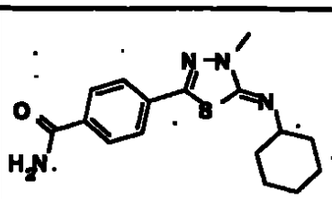
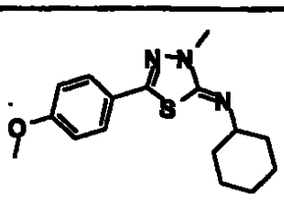
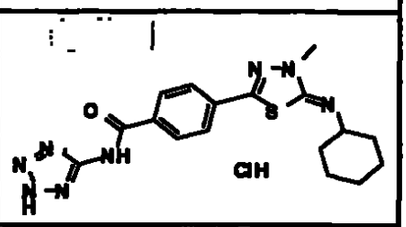
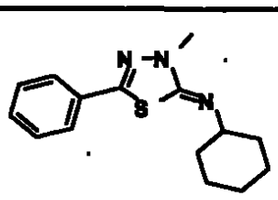
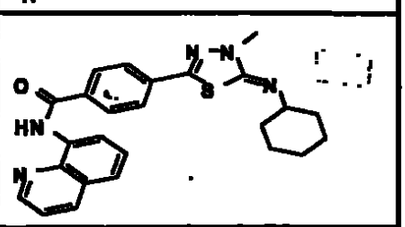
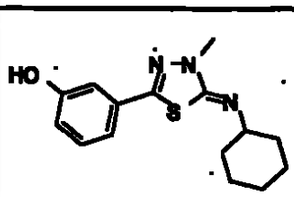
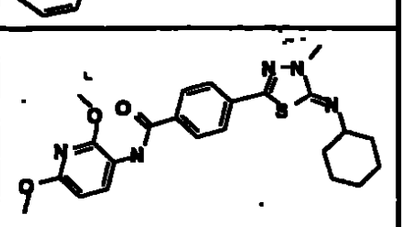
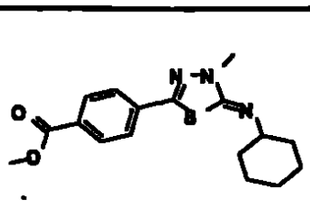
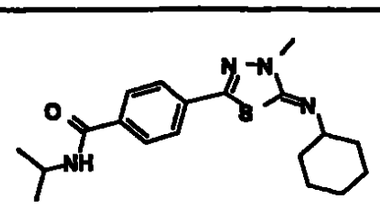
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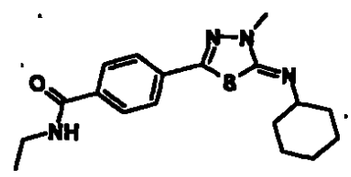
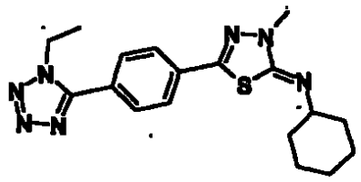
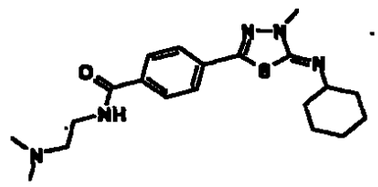
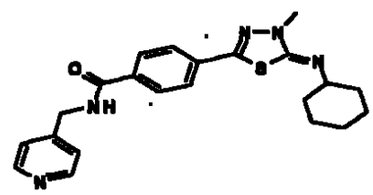
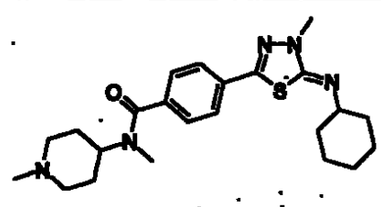
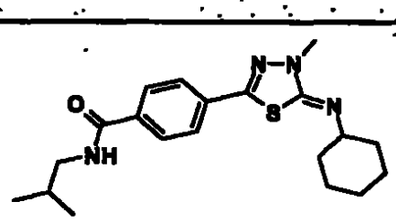
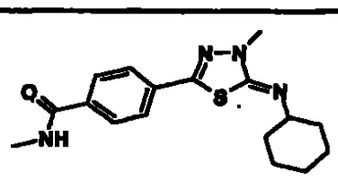
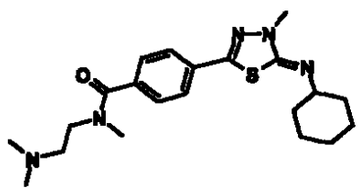
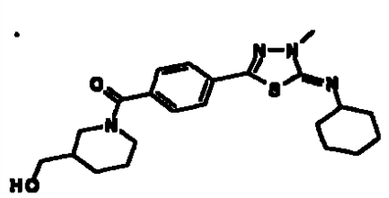
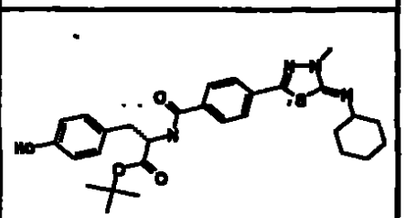
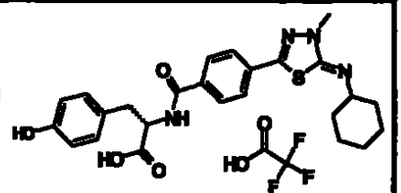
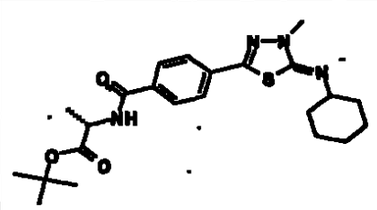
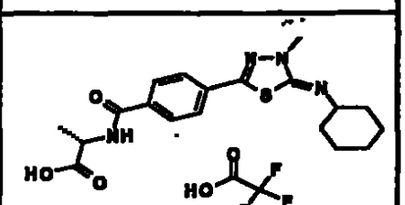
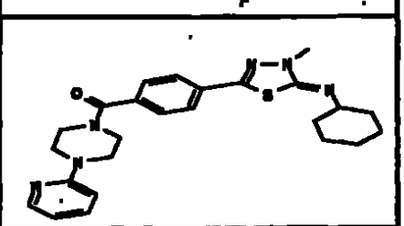
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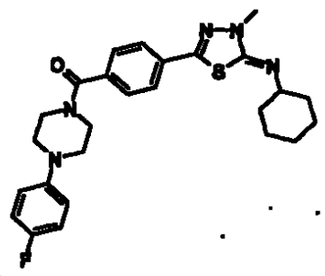
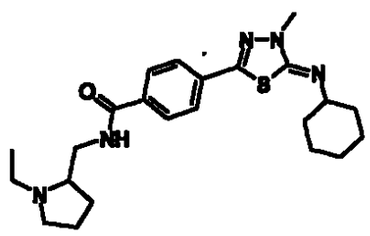
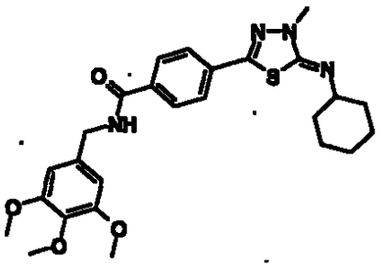
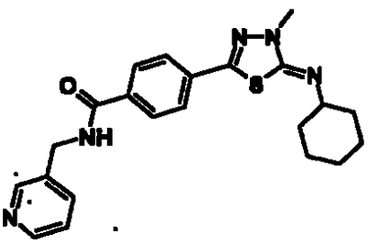
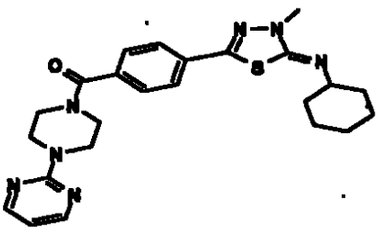
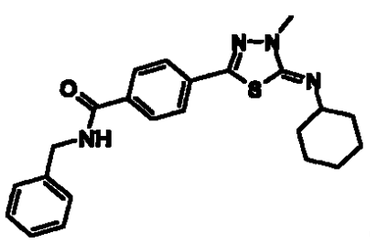
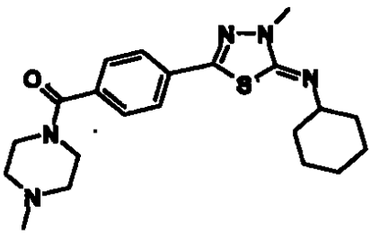
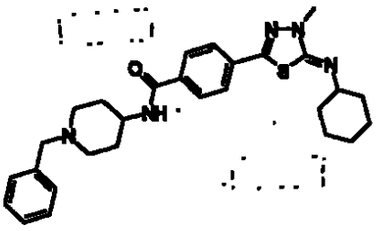
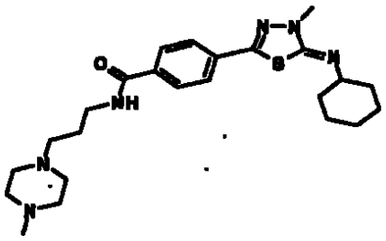
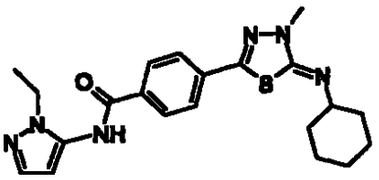
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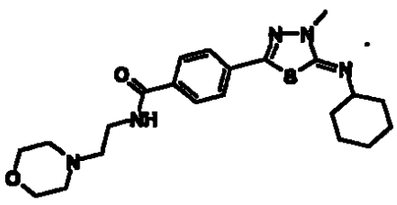
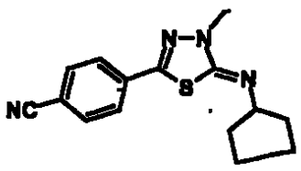
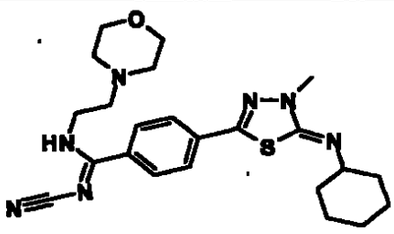
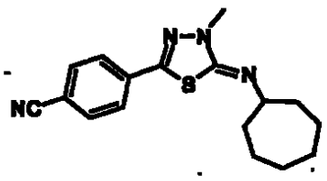
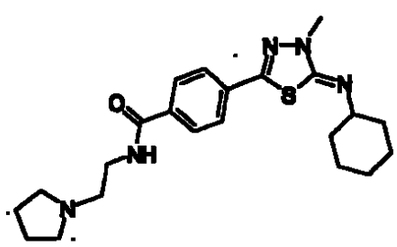
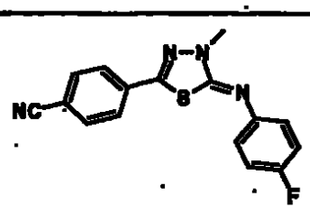
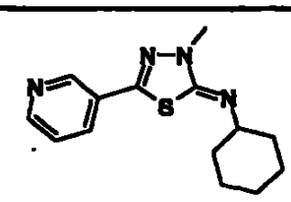
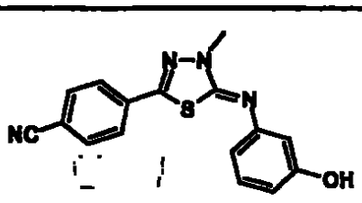
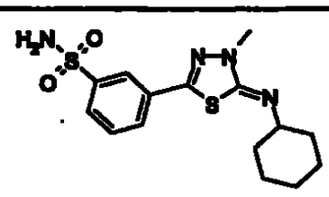
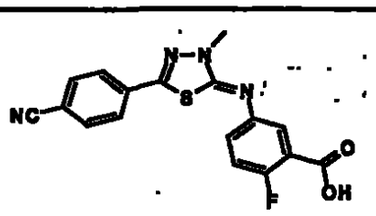
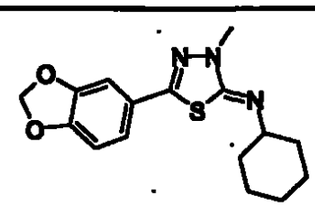
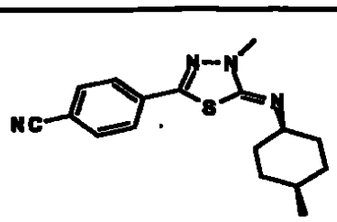
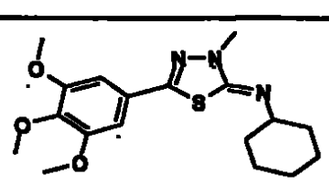
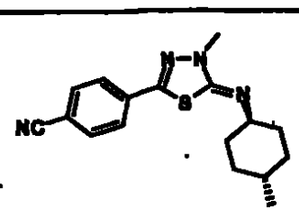
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I21	
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I21,2	
I21,3	
I21,4	

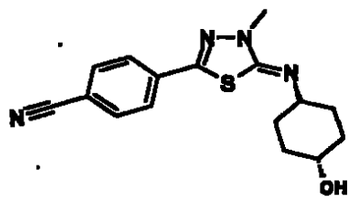
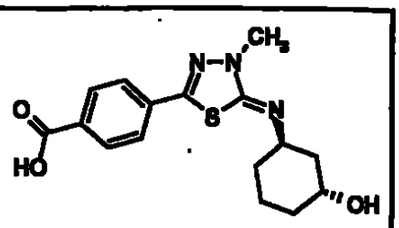
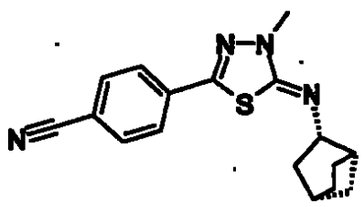
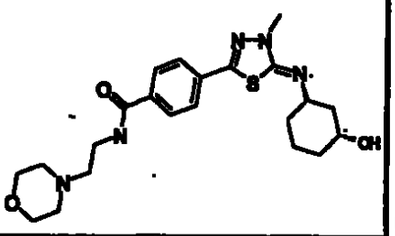
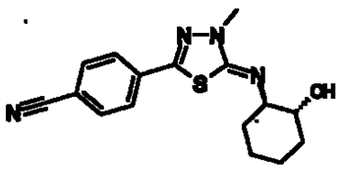
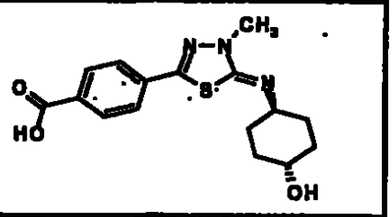
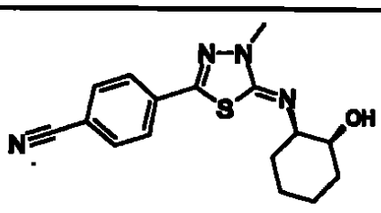
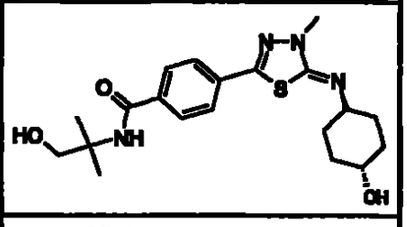
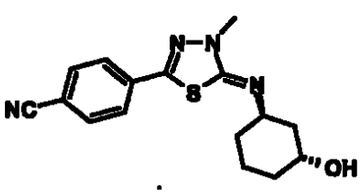
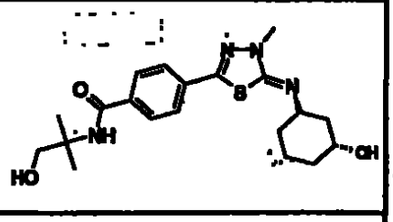
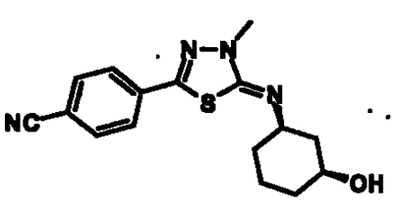
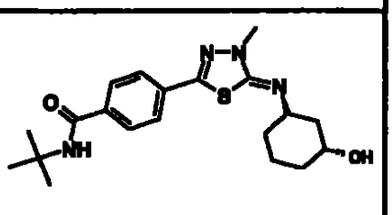
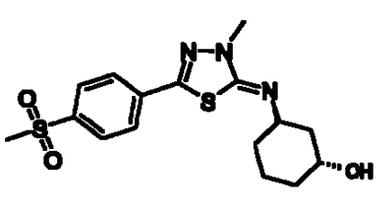
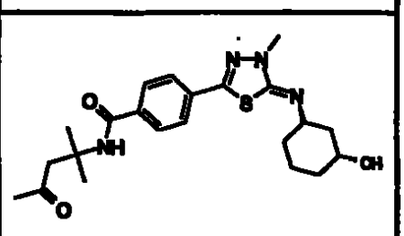
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I25		I31,1	
I26		I32	

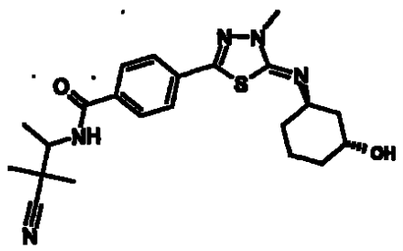
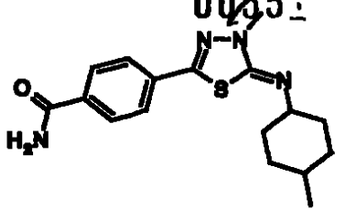
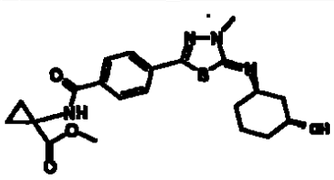
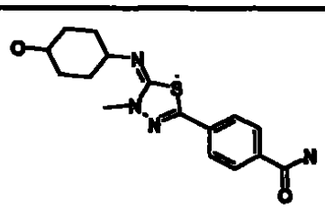
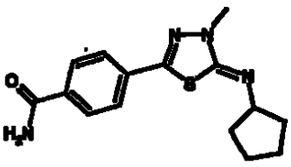
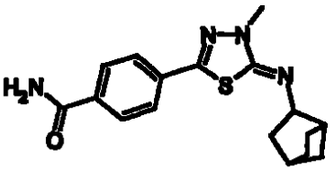
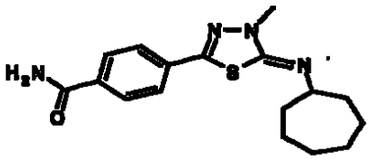
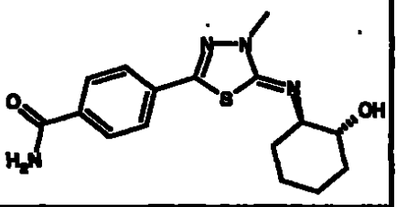
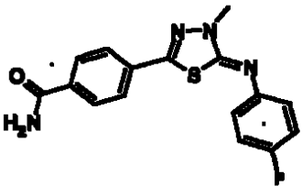
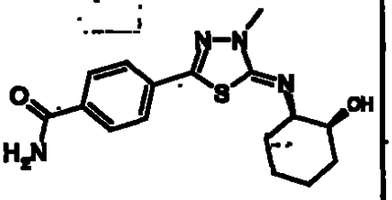
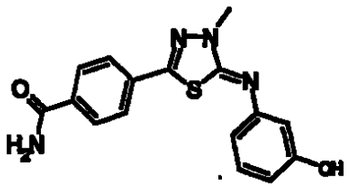
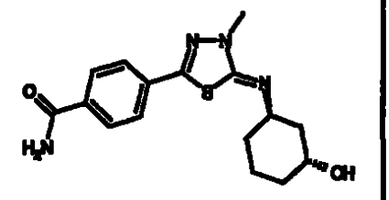
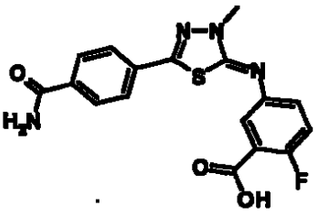
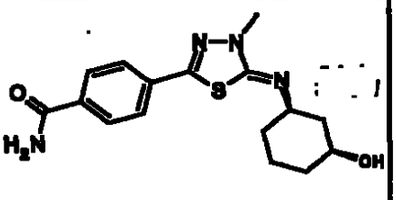
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I34		I37,2	
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I35,1		I37,4	
I35,2		I37,5	
I36		I37,6	
I37		I37,7	

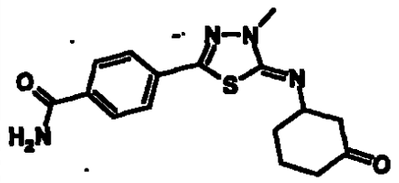
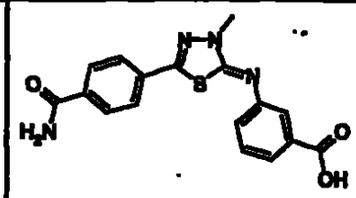
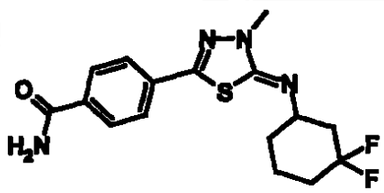
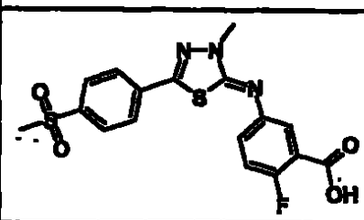
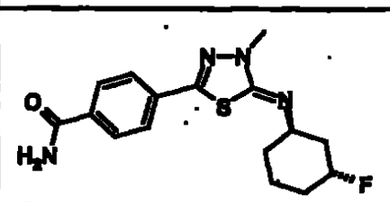
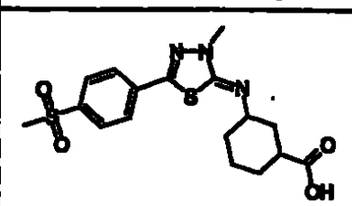
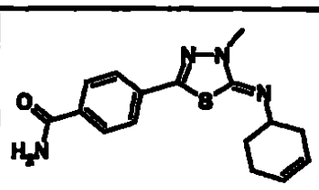
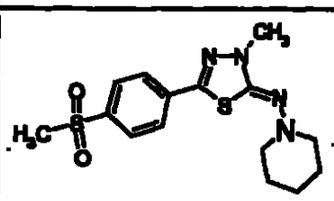
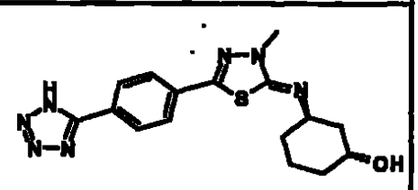
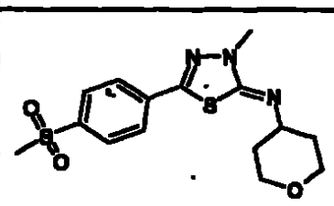
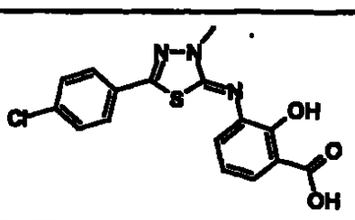
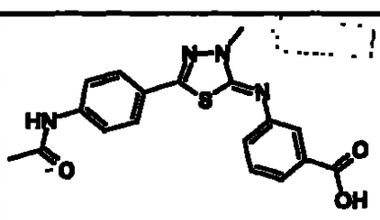
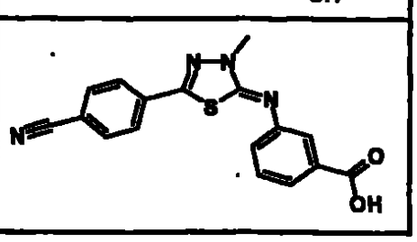
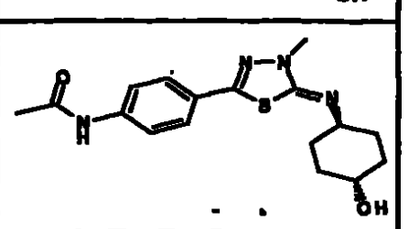
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I37,11	
I37,12	
I37,13	
I37,13-1	
I37,14	
I37,15	
I37,15-a	
I37,16	
I37,16-a	
I37,17	

I37,18		I37,23	
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I37,22		I37,27	

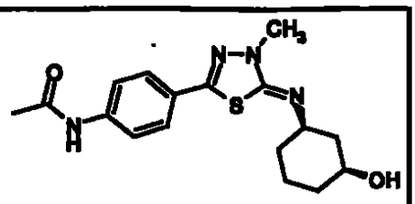
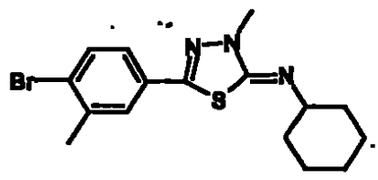
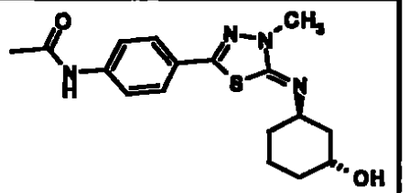
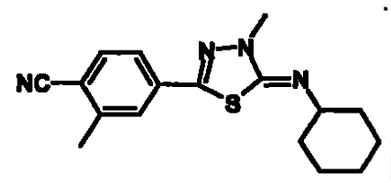
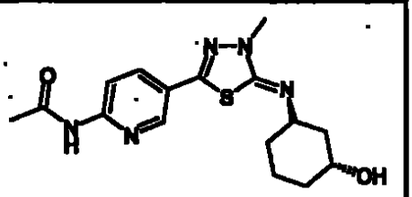
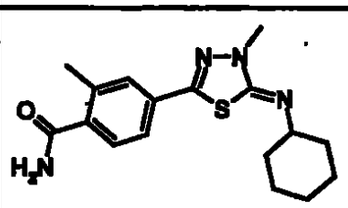
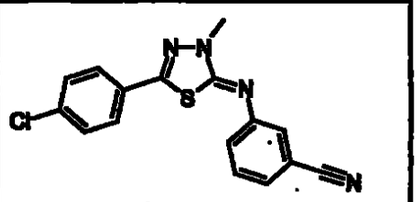
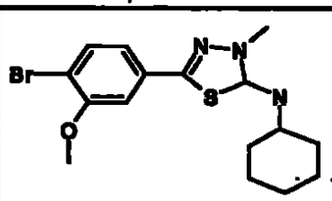
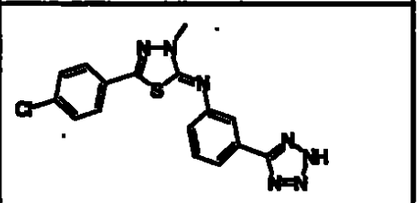
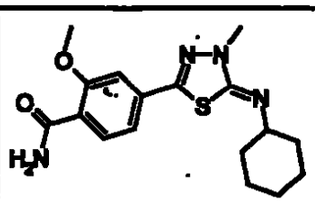
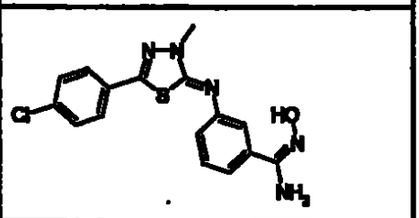
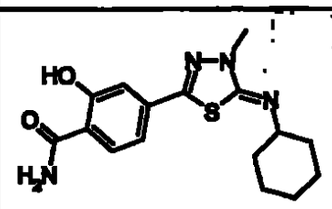
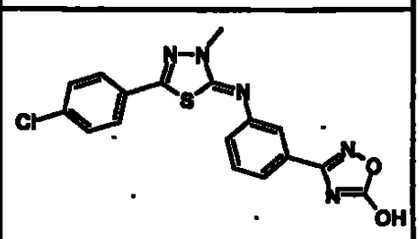
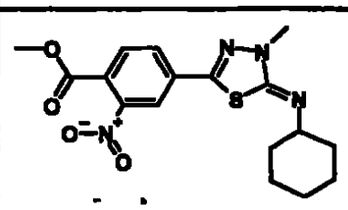
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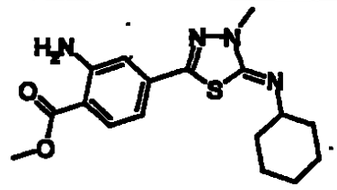
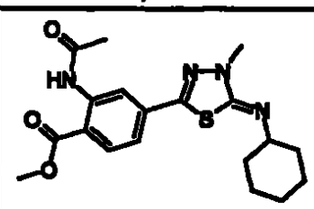
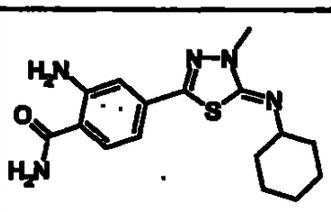
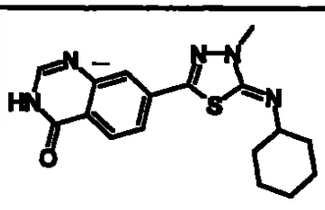
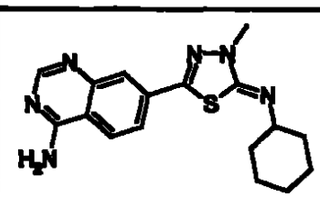
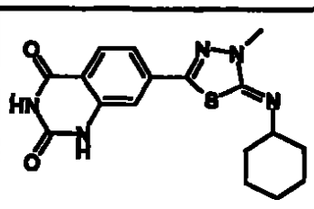
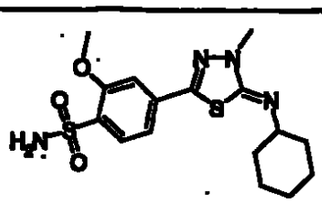
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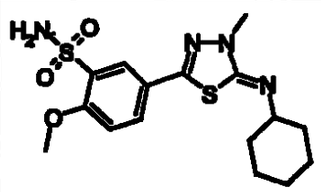
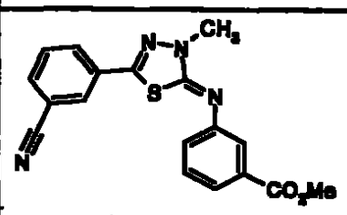
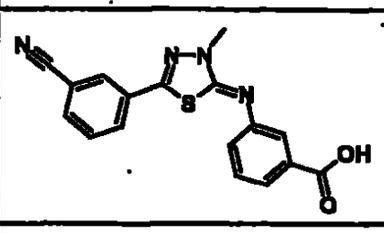
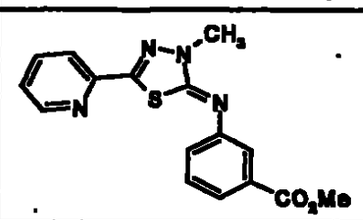
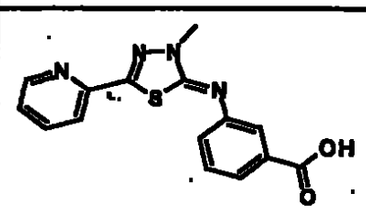
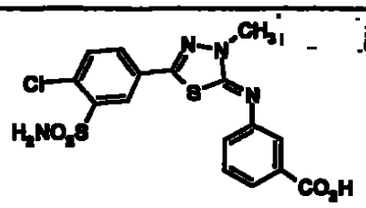
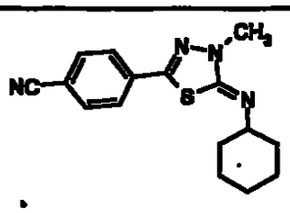
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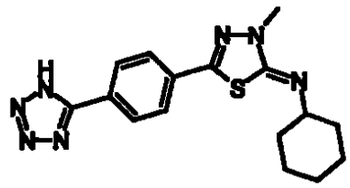
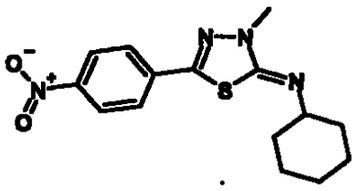
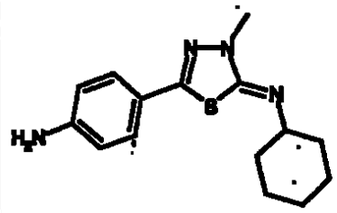
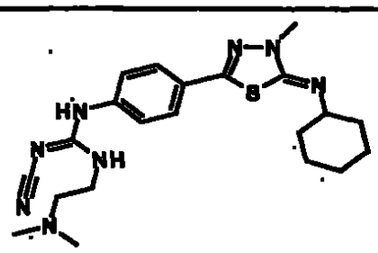
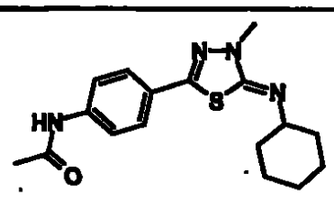
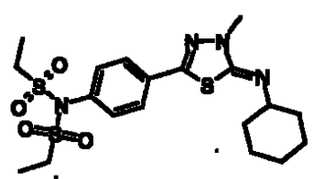
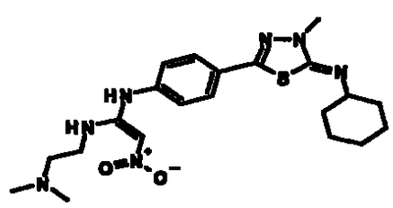
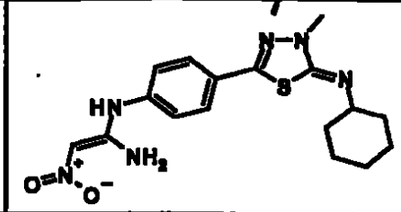
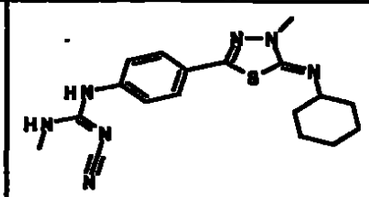
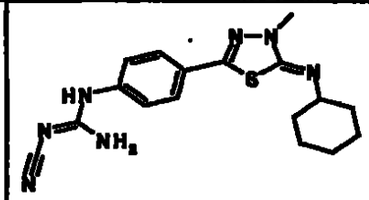
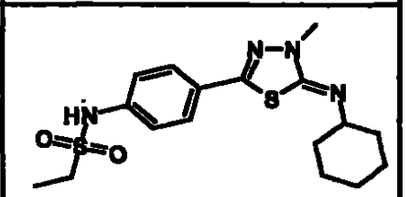
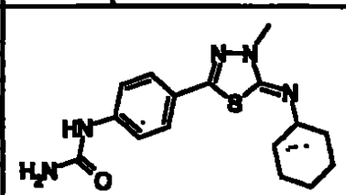
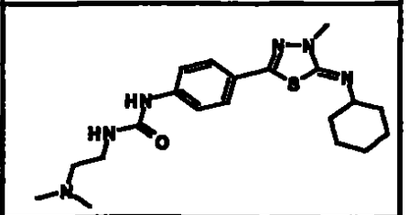
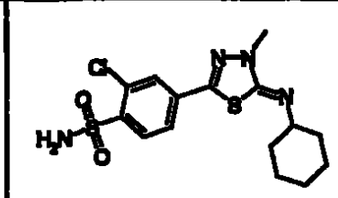
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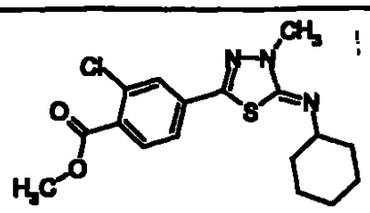
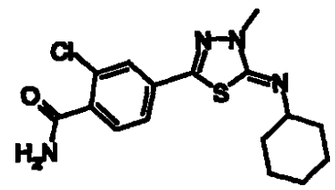
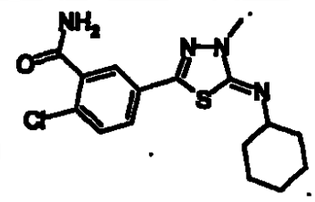
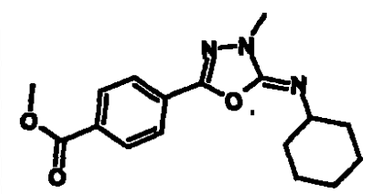
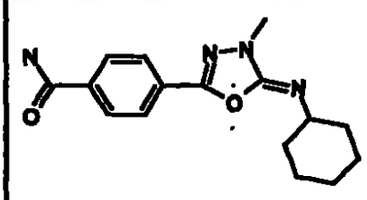
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I87		I91	
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I89		I91,2	
I90		I92	
I90,1		I92,1	
I90,2		I92,2	
I90,3		I93	

I93,1	
I93,2	
I93,3	
I93,4	
I93,5	
I93,6	
I94	

I95	
I96	
I96,1	
I97	
I97,1	
I98	
I99	

I99,1	
I100	
I100,1	
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I100,3	
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I100,6	
I100,7	
I100,8	
I100,9	
I100,10	
I100,11	
I101	

I102	
I102,1	
I103	
I104	
I104,1	

Biological results

In vitro inhibition of the phosphodiesterase 7 and of other phosphodiesterases

The capacity of the compounds of the invention to inhibit cyclic nucleotide phosphodiesterases was evaluated by measuring their IC_{50} (concentration necessary to inhibit the enzymatic activity by 50 %).

PDE3A3, PDE4D3, PDE7A1 were cloned and expressed in insect cells Sf21 using the baculovirus expression system. The source of PDE103 and of PDE503 were human cell lines

(respectively TPH1 human monocytes and MCF7 human caucasian breast adenocarcinoma). The various types f phosphodiesterases were obtained partially purified on an anion exchange column (Mono Q) according to a method adapted from Lavan B.E.,Lakey T., Houslay M.D. Biochemical Pharmacology, 1989, 38 (22), 4123-4136.

Measurement of the enzymatic activity for the various types f PDE was then made according to a method adapted from W.J. Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92,ed. G. Brooker et al. Raven Press, NY.

The substrate used was cGMP for PDE1 and PDE5 and cAMP f r PDE 3, PDE 4 and PDE 7. The substrate concentration was 0.2μM for PDE 1, PDE 3 and PDE 5, 0,25μM for PDE 4 and 50nM for PDE 7.

The enzymatic reaction was stopped after 1 hour for PDE 1, PDE 3 and PDE 5 and 10 minutes for PDE 4 and PDE 7.

In order to determine their IC_{50}, compounds of the invention were assayed at 8 concentrations ranging from 0.03nM to 100μM for PDE 4 and PDE 7 and at 6 concentration ranging from 0,1μM to 30μM for PDE 1, 3 and 5.

The IC_{50} (μM) were determined for some of the compounds f the invention, and the results are summarised in the following table:

Compounds	IC_{50} (PDE7)	Compounds	IC_{50} (PDE7)
I1	0,15	I27	0,46
I2,1	0,13	I28	0,23
I3,25	1,20	I29	0,30
I4	0,15	I30	0,14
I7	1,05	I31	0,23
I8	0,45	I32	0,23
I9	0,28	I33	0,24
I10,1	1,30	I34	0,63
I11	0,98	I35	0,58
I12	0,29	I36	0,29
I13	0,70	I37	0,23

selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_4-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
2) $COOR_5$, OR_5, SO_2R_5,
3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
    2) OR_5, $=NR_5$ or,
    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=N\text{-}SO_2NH_2)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$
  4) heterocycle optionally substituted with one or several groups R_5;

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl

optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-N(R_{18})(R_{19}) in which X_5 is a single bond or lower alkylene and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;

- X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{18})(R_{19}) in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;

- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

with the proviso that,

- when R1 is phenyl, it bears at least one substituent other than H,

- when X_2 is a single bond and both R1 and R'_3 are phenyl, each of R1 and R'_3 bear at least one substituent other than H,

- when X_2 is a single bond and R'_3 is phenyl, R'_3 is not substituted by an ester or a carboxylic acid in the ortho position,

- the atom of R3 which is linked to the thiadiazole group is a carbon atom,

with the exclusion of the following compounds,

1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiaz l-2-yl]-methanone,

1-[4-Phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-

ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,

1-Phenyl-1-(4-phenyl-5-*p*-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,

Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethyl-cyclopent-1-enylmethyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,

2-(3,5-Diphenyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,

2-[3-Phenyl-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,

2-[5-(1-Phenyl-methanoyl)-3-*p*-tolyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,

2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

2. A compound according to claim 1 in which R1, R2, R3 and Y are as defined in claim 1 with the proviso that, when R2 is a phenyl, unsubstituted or substituted whith 1 to 3 chorine or with a methyl, then R3 does not represent C(=O)-phenyl, C(=O)-thienyl, phenyl or CH_2-(2,3,3-trimethyl-cyclopent-1-enyl).

3. A compound of formula (I) as defined in claim 1 or 2, in which R1 is:

C_4-C_6 alkyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:
  1) H, =O, halogen, CN, lower haloalkyl, preferably

CF_3, lower alkyl, carboxylic acid bioisostere,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$,

wherein R_5 is selected from hydrogen or lower alkyl, optionally substituted with OH, and R_6, R_9 and R_{10} are identical or different and are selected from hydrogen or lower alkyl.

4. A compound as defined in any one of claims 1 to 3 in which R2 is lower alkyl.

5. A compound as defined in any one of claims 1 to 4 in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, and,
- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or lower alkylene, and,
- R_{17} is:

1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$,

$C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5.

6. A compound as defined in any one of claims 1 t 5, in which R1 is:

cycloalkyl, preferably cyclohexane,

cycloalkenyl,

aryl, preferably phenyl,

or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$.

  wherein R_5 and R_6 are identical or different and are selected from hydrogen or methyl.

7. A compound as defined in any one of claims 1 t 6, in which R2 is CH_3.

8. A compound as defined in any one of claims 1 t 7 in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,

aryl, preferably phenyl,

heterocycle,

or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or $-CH_2-$, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5.

9. A compound according to claims 3, 4 and 5.

10. A compound according to claims 6, 7 and 8.

11. A compound as defined in claim 1 in which

R1 is:

cyclohexane,

phenyl

or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:

1) H, halogen, CF_3,

2) COOH, OH,

3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same r different and are selected from H or lower alkyl,

R2 is CH_3, and,

R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

phenyl

heterocycle,

or a polycyclic group;

each optionally substituted with one r several groups X_3-R_{17},

identical or different, in which:

- X_3 is a single bond, and,
- R_{17} is:
  1) CN, OH, CF_3, =O, C_1-C_6 alkoxy, halogen,
  2) $COOR_5$, SO_2R_5,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 or R_6,
  4) heterocycle optionally substituted with one or several groups R_5.

12. A compound as defined in any one of claims 1 to 11 in which Y is S.

13. A compound as defined in any one of claims 1 t 11 in which Y is O.

14. A compound selected from the group consisting of:
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol,
2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol,
{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-propyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,

[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol,
tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-isopropyl-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine,
(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine,
3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
5-[5-(4-Chl ro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,

(1-Aza-bicyclo[2.2.2] ct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine,
(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide,
Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol,
3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid,
(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine,
(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[5-(3-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiaz l-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiaz l-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiaz l-2-yl)-2,3-dimethoxy-phenol,
compound with trifluoro-methanesulfonic acid
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,

{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,

C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,

2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide,

[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester,

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz l-2-yl)-benz ic acid methyl ester,

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol,
6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol,
Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol,
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol,
compound with 1,1,1-trifluoro-methanesulfonic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid;
Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2H-tetrazol-5-yl)-benzamide hydrochloride salt,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
2-({1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-methanoyl}-amino)-3-(4-hydroxy-phenyl)-propionic acid, compound with 2,2,2-trifluoro-acetic acid,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,

[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,

N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,

N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,

[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,

Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,

(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine,

Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
5-[5-(4-Cyano-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-(trans-4-Hydroxy-cycl hexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,

4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,

N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester,

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,

4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,

4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,

4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
(1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine,
[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine,
3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,
N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,
N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,
N-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide,
3-[5-(4-Chloro-phenyl)-3-methyl-3H/-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile,

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine,
3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol,
[5-(4-Bromo-3-methyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide,
[5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester,

3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine,
[5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide,
[5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
(E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine,
[5-(*N*-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-urea,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz 1-2-yl)-benzenesulfonamide,

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2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiaz l-2-yl)-benzoic acid methyl ester, and,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide.

15. A compound according to claim 14, selected from the group consisting of:

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiaz l-2-yl)-N-ethyl-N-(2-morpholin-4-yl-

ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid; compound with 2,2,2-trifluoro-acetic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,
N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cycl hexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinaz lin-4-one,

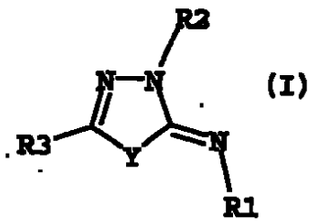
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7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,.

N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide, and,

1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea.

16. Pharmaceutical composition comprising a compound of formula (I),



(I)

wherein:

- Y is O or S;
- R1 is:
  - C_1-C_{10} alkyl,
  - C_2-C_{10} alkenyl,
  - C_2-C_{10} alkynyl,
  - cycloalkyl,
  - cycloalkenyl,
  - heterocycle,
  - aryl,
  - or a polycyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or a divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower

alkyl, carboxylic acid bioisostere,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_2-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,

2) OR_5, $=NR_5$ or,

3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R'3 is:

cycloalkyl,

cycloalkenyl,

aryl,

heterocycle,

or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:

a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene, a divalent heterocycle or a divalent polycyclic group, and,

- R_{17} is:

1) H, $=O$, NO_2, CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

4) heterocycle optionally substituted with one or several groups R_5;

wherein,

- R_5 and R_6 are the same or different and are selected from :

- H,

- lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
- X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

each optionally substituted with one or several groups which are the same or different and which are selected from:

- halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}; C(=O)-lower alkyl, lower haloalkyl, X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkyl and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;
- X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;
- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier, with the proviso that the compound of formula (I) is not 4-[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-butyric acid ethyl ester, or, 4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-butyric acid ethyl ester.

17. A pharmaceutical composition according to claim 16,

comprising a compound of formula (I), in which R1, R2, R3 and Y are as defined in claim 18, with the proviso that when R1 is C(=O)-H, then R2 does not represent $(CH2)_3$-C(=O)OCH_2CH_3.

18. Pharmaceutical composition comprising a compound f formula (I) according to any one of claims 1 to 15, together with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to claim 16, 17 or 18, for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant.

20. Method for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant, comprising administering to a mammal, particularly a human, in need thereof, an effective amount of compound of formula (I) according any of claims 1 to 15.

21. Method according to claim 20, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

22. Method according to claim 20, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

23. Use of a compound of formula (I) according to any one of claims 1 to 15, for the manufacture of a medicament for the treatment of diseases for which treatment by a PDE7 inhibitor is relevant.

24. Use according to claim 23, in which the disease to be treated is selected from T-cell-related diseases,

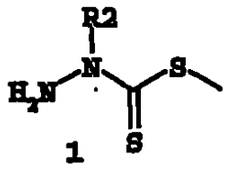
autoimmune diseases, inflammat ry diseases, respirat ry diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

25. Use according to claim 23, in which the disease t be treated is selected from visceral pain, inflammat ry bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

26. A compound of formula (I) as defined in any one of claims 1 to 15, as a medicament.

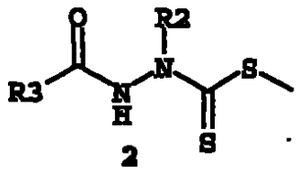
27. A process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15 in which Y is S, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with carbon disulphide and MeX where X is a leaving group to obtain a compound of formula 1



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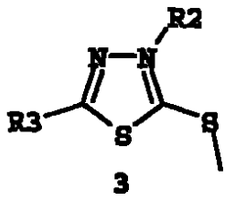
(b) reaction of the S-methyldithiocarbazate 1 with an acyl chloride R3COCl in which R3 is as defined in claim 1 t to obtain an acylated methyldithiocarbazate 2.



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(c) cyclization of the acylated methyldithiocarbazate 2 into a 1,3,4-thiadiazole 3

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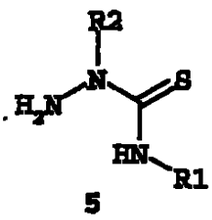
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(d) reaction of the 1,3,4-thiadiazole 3 with an amine $R1NH_2$ in which R1 is as defined in claim 1, to obtain the compound of formula (I) in which Y is S,

(e) isolating the compound of formula (I).

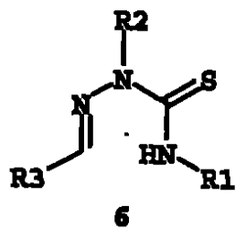
28. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1 in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5



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(b) reaction of the thiosemicarbazide 5 with an aldehyde R3CHO in which R3 is as defined in claim 1, to obtain the thiosemicarbazone 6



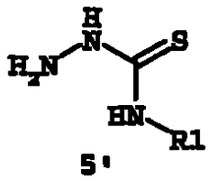
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(c) cyclization of the thiosemicarbazone 6 into the compound of formula (I) in which Y is S,

(d) isolating the compound of formula (I).

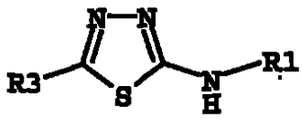
29. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH in which R3 is as defined in claim 1, with the following thiosemicarbazide 5'



5'

to obtain the 1,3,4-thiadiazole 7



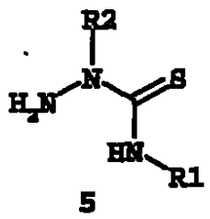
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(b) reaction of the 1,3,4-thiadiazole 7 with R2X, in which R2 is as defined in claim 1 and X is a leaving group to obtain the compound of formula (I) in which Y is S

(c) isolating the compound of formula (I).

30. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH, in which R3 is as defined in claim 1, with the following thiosemicarbazide 5



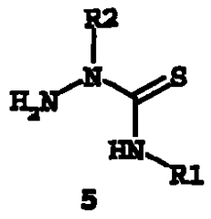
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to obtain the final compound of formula I in which Y is S,

(b) isolating the compound of formula (I).

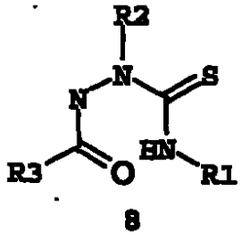
31. Process for the preparation of a 1,3,4-oxadiazole f formula (I) according to any one of claims 1 to 11 or 13, in which Y is O, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$, in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1, in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5,



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(b) reaction of the thiosemicarbazide 5 with R3-C(=O)Cl, in which R3 is as defined in claim 1, to form the desired thiosemicarbazide 8



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(c) cyclization of the thiosemicarbazide 8 into the final compound of formula I in which Y is O,

(d) isolating the compound of formula (I).

INTERNATIONAL SEARCH REPORT

Ir' ational Application No
Iv1/EP 01/11330 00571

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D285/135 C07D271/113 C07D417/04 C07D417/10 C07D417/12
C07D417/14 C07D453/02 A61K31/433 A61K31/55 A61K31/439
A61K31/4245 A61K31/4439 A61K31/4709 A61K31/497 A61P29/00

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)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 120, no. 25, 20 June 1994 (1994-06-20) Columbus, Ohio, US; abstract no. 323458w, EL-FEKY S A ET AL: "Synthesis and biological activity of novel quinazolinones derived from 2-hydrazino-3-phenyl-4(3H)-quinazolinones" page 907; XP002162034 abstract -& DATABASE CAPLUS 'Online! Chemical Abstracts Services; Database accession no. 1994:323458 XP002162039 * RN 155389-95-0 and 155389-96-1 * & ZHONGHUA YAOXUE ZAZHI, vol. 45, no. 4, 1993, pages 303-308,	16-19

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in 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
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Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2001	21/12/2001

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/11330

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P37/00

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DD 251 979 A (PÄDAGOGISCHE HOCHSCHULE "DR. THEODOR NEUBAUER", ERFURT/MÜHLHAUSEN) 2 December 1987 (1987-12-02) the whole document	1-11,13, 31
X	HUISGEN R ET AL: "1.3-Dipolare Cycloadditionen. VI. Anlagerung der Nitrilimine an azomethine und Isocyanate" CHEMISCHE BERICHTE, vol. 97, no. 4, 3 April 1964 (1964-04-03), pages 1085-1095, XP002185163 the whole document, particularly page 1087, compound XXVI	1-11,13, 31

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in 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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2001	

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/11[illegible]0572

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L'ABBÉ G ET AL: "Synthesis and decomposition of functionalized diaziridinimines" JOURNAL OF ORGANIC CHEMISTRY, vol. 46, no. 22, 23 October 1981 (1981-10-23), pages 4478-4481, XP002185164 the whole document, particularly page 4479, compound 15b	1-11,13, 31
X	CHEMICAL ABSTRACTS, vol. 73, no. 11, 14 September 1970 (1970-09-14) Columbus, Ohio, US; abstract no. 56035q, GEHLEN H ET AL: "2-Amino-1,3,4-oxadiazoles. XXXV. Synthesis and reaction of 1,3,4-oxadiazolo'3,2-a!pyrimidinones" page 322; XP002185165 abstract & ARCH. PHARM. (WEINHEIM), vol. 303, no. 6, 1970, pages 501-510,	1-11,13, 31
X	AWASTHI A K AND AL: "A new route to 2,3,5-trisubstituted 2,3-dihydro-1,3,4-oxadiazoles via stabilized sulfuranes" SYNTHESIS, no. 7, July 1984 (1984-07), pages 590-591, XP002185166 the whole document	1-11,13, 31
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATI NAL SEARCH REPORT

Information on patent family members

International Application No
F../EP 01/11330

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
DD 251979	A	02-12-1987	DD	251979 A1	02-12-1987
WO 9942089	A	26-08-1999	AU	2926099 A	06-09-1999
			WO	9942089 A2	26-08-1999
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			DE	3717232 A1	08-12-1988
			JP	1031788 A	02-02-1989

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(19) ORGANIZACIÓN MUNDIAL DE LA PROPIEDAD INTELECTUAL

Oficina Internacional

[aparece el sello de la OMPI]

[aparece un código de barras]

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(10) Número de publicación internacional: **WO 02/28847 A1**

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(51) Clasificación Internacional de Patentes[7]: **C07D 285/135, 271/113, 417/04, 417/10, 417/12, 417/14, 453/02, A61K 31/433, 31/55, 31/439, 31/4245, 31/4439, 31/4709, 31/497, A61P 29/00, 37/00**

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(81) Estados Designados (nacionales): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Declaraciones conforme a la Norma 4.17

- *sobre el derecho del solicitante a solicitar y que le sea otorgada una patente (Norma 4.17(ii)) para las siguientes designaciones AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Patente de Eurasia (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).*

- *sobre el derecho del solicitante de reivindicar la prioridad de la solicitud anterior (Norma 4.17(iii) para la siguiente designación US*

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- sobre el derecho del solicitante de reivindicar la prioridad de la solicitud anterior (Norma 4.17(iii) para la siguiente designación US

- sobre el derecho del solicitante de reivindicar la prioridad de la solicitud anterior (Norma 4.17(iii) para la siguiente designación US

- sobre el derecho del solicitante de reivindicar la prioridad de la solicitud anterior (Norma 4.17(iii) para la siguiente designación US

- sobre el derecho del solicitante de reivindicar la prioridad de la solicitud anterior (Norma 4.17(iii) para la siguiente designación US

- de inventor (Norma 4.17(iv) para US solamente

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- con informe de búsqueda internacional.

Para los códigos de dos letras y otras abreviaturas, consultar las "Notas de Guía sobre Códigos y Abreviaturas" que aparecen al comienzo de cada edición periódica del Boletín del PCT.

(54) Título: NUEVOS TIADIAZOLES Y OXADIAZOLES Y SU USO COMO INHIBIDORES DE FOSFODIESTERASA-7

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(57) Resumen de la invención: La invención proporciona 1,3,4-tiadiazoles y 1,3,4-oxadiazoles que tienen la siguiente fórmula (I): en donde Y es S u O, R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, cicloalquenilo, arilo, heteroarilo o un grupo policíclico, optativamente sustituido, R_2 es alquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, cicloalquenilo o arilo optativamente sustituido, R_3 es X_2-R'_3, en donde X_2 es un grupo de unión y R'_3 es cicloalquilo, heterocicloalquilo, cicloalquenilo, arilo, heteroarilo, o un grupo policíclico, optativamente sustituido, o sus derivados farmacéuticamente aceptables, el proceso para su preparación y sus uso para la fabricación de un medicamento para el tratamiento de trastornos para los cuales el tratamiento con un inhibidor de PDE7 es relevante.

NUEVOS TIADIAZOLES Y OXADIAZOLES Y SU USO COMO INHIBIDORES DE FOSFODIESTERASA-7

Campo de la Invención

La invención se relaciona con tiadiazoles y oxadiazoles novedosos, procesos para su preparación y su uso como inhibidores de fosfodiesterasa 7 (PDE7).

Antecedentes de la Invención

Las fosfodiesterasas (PDE) juegan un importante papel en diversos procesos biológicos hidrolizando los segundos mensajeros claves monofosfatos 3',5'-cíclicos de adenosina y guanosina (cAMP y cGMP respectivamente) en sus nucleótidos de 5'-monofosfato correspondientes. En consecuencia, la inhibición de la actividad de PDE produce un aumento de los niveles intracelulares de cAMP y cGMP que activan las vías de fosforilación de proteínas específicas involucradas en una variedad de respuestas funcionales.

Se han identificado al menos once isoenzimas fosfodiesterasas de nucleótidos cíclicos de mamíferos, numeradas PDE 1 a PDE 11, sobre la base de la estructura primaria, la especificidad

de sustrato o la sensibilidad a cofactores o drogas inhibidoras.

Entre estas fosfodiesterasas, PDE7 es una PDE específica de cAMP. La caracterización bioquímica y farmacológica mostrada como PDE específica de cAMP de alta afinidad (Km=0,2 μM), que no se vio afectada por los inhibidores de la isoenzima PDE selectiva potente de cGMP.

Se ha detectado actividad o proteína de PDE7 en cultivos de células T, cultivos de células B, cultivos de células epiteliales de las vías respiratorias (AE) y varios tejidos fetales.

El aumento de los niveles de cAMP por la inhibición selectiva de PDE7 parece ser un enfoque potencialmente prometedor para bloquear específicamente las respuestas inmunes mediadas por células T. Otros estudios han demostrado que la elevación de los niveles intracelulares de cAMP puede modular procesos inflamatorios e inmunológicos. Este enfoque selectivo podría presumiblemente estar despojado de los efectos colaterales asociados con los inhibidores selectivos (ej. los inhibidores selectivos de PDE3 o PDE4) y que limitan su uso.

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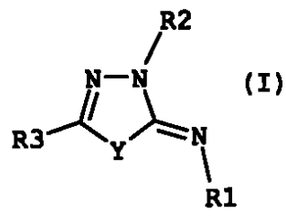
También se ha revelado un papel funcional de la PDE7 en la activación de las células T; en consecuencia los inhibidores selectivos de PDE7 serían candidatos para el tratamiento de enfermedades relacionadas con las células T.

Las células AE participan activamente en las enfermedades inflamatorias de vías respiratorias liberando mediadores tales como metabolitos de araquidonato y citocinas. La inhibición selectiva de PDE7 puede ser un enfoque antiinflamatorio útil para tratar las enfermedades relacionadas con las células AE.

Por lo tanto, existe una necesidad de inhibidores selectivos de PDE7, que sean activos a muy bajas concentraciones, es decir inhibidores micromolares, preferentemente inhibidores nanomolares.

Resumen de la Invención

La invención proporciona composiciones farmacéuticas que comprenden un compuesto que tiene la siguiente fórmula (I):



en donde:

- Y es O o S;
- R_1 es:

  alquilo de C_1-C_{10},

  alquenilo de C_2-C_{10},

  alquinilo de C_2-C_{10},

  cicloalquilo,

  cicloalquenilo,

  heterociclo,

  arilo,

  o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

  alquilo inferior,

  alquenilo de C_2-C_{10},

  alquinilo de C_2-C_{10},

  cicloalquilo,

  cicloalquenilo,

  heterociclo,

  arilo;

  cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

  1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

  2) $COOR_5$, OR_5, SO_2R_5,

  3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es X_2-R'_3 en donde:

- X_2 es un solo enlace o,

  un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

  1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo,

heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo heterocíclico divalente, y

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, bioisóstero de ácido carboxílico, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o

diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

en donde,

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenilo de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-$N(R_{18})(R_{19})$

en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policiclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos optativamente se sustituyen con uno o varios grupos, idénticos o diferentes, seleccionados

de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o $X_5-N(R_{19})-R_{18}$ en donde X_5 es un solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;
- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

junto con un portador farmacéuticamente aceptable,

con la condición de que el compuesto de la fórmula (I) no sea etil éster del ácido 4-[2-Formilimino-5-(4-metoxi-fenil)-[1,3,4] tiadiazol-3-il]-butírico,

etil éster del ácido 4-[5-(4-cloro-fenil)-2-formilimino-[1,3,4]tiadiazol-3-il]-butírico.

La invención también se relaciona con compuestos novedosos que tienen la fórmula (I) precedente.

Estos compuestos son inhibidores selectivos de PDE7. Pueden usarse en el tratamiento de diversas enfermedades, tales como enfermedades relacionadas con células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades

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respiratorias, enfermedades del sistema nervioso central (CNS), enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, enfermedades gastrointestinales, dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA) o rechazo de trasplantes.

La invención también se relaciona con un proceso para preparar los compuestos precedentes.

La invención además se relaciona con el uso de un compuesto de la fórmula (I) para la preparación de un medicamento para la prevención o el tratamiento de trastornos para los cuales la terapia con un inhibidor de PDE7 es relevante.

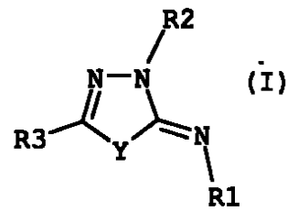
La invención también proporciona un método para el tratamiento de un trastorno para el cual la terapia con un inhibidor de PDE7 es relevante, que comprende administrar a un mamífero que lo necesita una cantidad efectiva de un compuesto de la fórmula (I).

La invención también se relaciona con una composición farmacéutica que comprende un compuesto de la fórmula (I) jutno con un portador farmacéuticamente aceptable.

La invención también se relaciona con una composición farmacéutica para el tratamiento de un trastorno para el cual la terapia con un inhibidor de PDE7 es relevante, que comprende un compuesto de la fórmula (I) junto con un portador farmacéuticamente aceptable.

Descripción Detallada de la Invención

La presente invención proporciona composiciones farmacéuticas que comprenden compuestos que tienen la fórmula (I),



en donde R_1, R_2, R_3 e Y son lo definido anteriormente con la exclusión de los compuestos mencionados anteriormente.

En el texto siguiente y precedente:

- arilo se refiere a un carbociclo insaturado, que comprende exclusivamente átomos de carbono en la estructura cíclica, cuyo número es entre 5 y 10, que incluye fenilo, naftilo o tetrahidronaftilo;

- heterociclo se refiere a un monociclo no saturado o saturado que contiene entre 1 y 7 átomos de carbono en la

estructura cíclica y por lo menos un heteroátomo en la estructura cíclica, tal como nitrógeno, oxígeno, o azufre, preferentemente de 1 a 4 heteroátomos, idénticos o diferentes, seleccionados de átomos de nitrógeno, azufre y oxígeno. Los heterociclos adecuados incluyen morfolinilo, piperazinilo, pirrolidinilo, piperidinilo, pirimidinilo, 2- y 3-furanilo, 2- y 3-tienilo, 2-piridilo, 2- y 3-piranilo, hidroxipiridilo, pirazolilo, isoxazolilo, tetrazol, imidazol, triazol y similares;

- grupos policíclicos incluyen por lo menos dos ciclos, idénticos o diferentes, seleccionados de grupos arilo, heterociclo, cicloalquilo, cicloalquenilo fusionados juntos para formar dicho grupo policíclico tal como 2- y 3-benzotienilo, 2- y 3-benzofuranilo, 2-indolilo, 2- y 3-quinolinilo, acridinilo, quinazolinilo, indolilo benzo[1,3]dioxolilo y 9-tioxantanilo;
Los grupos policíclicos más preferidos incluyen 2 ciclos (sustituyentes bicíclicos) definidos anteriormente.

- grupos bicíclicos se refieren a dos ciclos, que son iguales o diferentes y que se eligen de arilo, heterociclo, cicloalquilo o cicloalquenilo, fusionados juntos para formar dichos grupos bicíclicos;

- halógeno se refiere a flúor, cloro, bromo o yodo;

- alquilo inferior significa que el alquilo es lineal o ramificado y contiene de 1 a 6 átomos de carbono; ejemplos de

grupos alquilo inferior incluyen metilo, etilo, propilo, butilo, isopropilo, terc-butilo, isobutilo, n-butilo, pentilo, hexilo y similares.

- alquenilo se refiere a una cadena de átomos de carbono insaturados, lineales o ramificados, que comprende uno o varios enlaces dobles, preferentemente que comprende uno o dos enlaces dobles. Los alquenilos preferidos comprenden de 3 a 6 átomos de carbono y un enlace doble.

- alquinilo se refiere a una cadena de átomos de carbono insaturados lineales o ramificados, que comprende uno o varios enlaces triples, preferentemente uno o dos enlaces triples. Los alquinilos preferidos comprenden de 3 a 6 átomos de carobno y un enlace triple.

- haloalquilo inferior se refiere a un alquilo inferior sustituido con uno o varios halógenos. Los grupos haloalquilo inferiores preferidos incluyen grupos perhaloalquilo tales como CF_3.

- cicloalquilo se refiere a un monocarbociclo saturado que contiene de 3 a 10 átomos de carbono; grupos cicloalquilo preferidos comprenden ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

- cicloalquenilo se refiere a un monocarbociclo insaturado que contiene de 3 a 10 átomos de carbono. Grupos cicloalquenilo preferidos contienen 1 o 2 enlaces dobles. Ejemplos de cicloalquenilo adecuados son 3-ciclohexeno, 3-ciclohepteno o

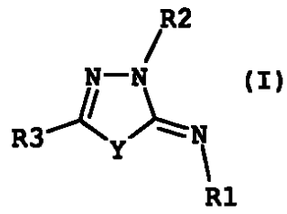
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similares.

- el bioisóstero de ácido carboxílico tiene el significado clásico; bioisósteros de ácido carboxílico comunes son tetrazol, ácido hidroxámico, isoxazol, hidroxitiadiazol, sulfonamida, sulfonilcarboxamida, fosfonatos, fosfonamidas, fosfinatos, sulfonatos, acil sulfonamida, mercaptoazol, acil cianamidas.

Las composiciones farmacéuticas preferidas son aquellas que contienen un compuesto de la fórmula (I) en donde R_1, R_2, R_3 e Y son lo definido anteriormente, con la condición de que cuando R_1 es C(=O)-H, entonces R_2 no representa $(CH_2)_3$-C(=O)OCH_2CH_3.

La presente invención también se relaciona con compuestos de la fórmula (I),



en donde

- Y es O o S;
- R_1 es:

  alquilo de C_4-C_{10},

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y,

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

  alquilo inferior,

  alquenilo de C_2-C_{10},

  alquinilo de C_4-C_{10},

  cicloalquilo,

  cicloalquenilo,

  heterociclo,

  arilo;

  cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

  1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

  2) $COOR_5$, OR_5, SO_2R_5,

  3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es X_2-R'_3 en donde:

- X_2 es un solo enlace o,

  un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se

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seleccionan de:

1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo policíclico divalente, y,

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

en donde, R_5, R_6, R_9 y R_{10} son lo definido anteriormente,

con la condición de que,

- cuando R_1 es fenilo, lleva por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y tanto R_1 como R'_3 son fenilo, cada uno de R_1 y R'_3 llevan por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y R'_3 es fenilo, R'_3 no se sustituye con un éster o un ácido carboxílico en la posición orto,

- el átomo de R_3 que está unido al grupo tiadiazol es un átomo de carbono,

excluyendo los siguientes compuestos,

1-Fenil-1-[4-fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-metanona,

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1-[4-Fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-1-tiofen-2-il-metanona,

1-Fenil-1-(4-fenil-5-*p*-tolilimino-4,5-dihidro-[1,3,4]tiadiazol-2-il)-metanona,

Ciclohexil-[3-(2,4,6-tricloro-fenil)-5-(2,3,3-trimetil-ciclopent-1-enilmetil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

2-(3,5-Difenil-3*H*-[1,3,4]tiadiazol-2-ilidenamino)-1,4-difenil-but-2-en-1,4-diona,

Dimetil éster del ácido 2-[3-Fenil-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico,

Dimetil éster del ácido 2-[5-(1-Fenil-metanoil)-3-*p*-tolil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico, y,

Dimetil éster del ácido 2-[3-(4-Cloro-fenil)-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico.

Los compuestos preferidos de la fórmula (I) son aquellos en los cuales R_1, R_2, R_3 e Y son lo definido anteriormente, con la condición de que, cuando R_2 es fenilo, no sustituido o sustituido con 1 a 3 cloro o con un metilo, entonces R_3 no representa C(=O)-fenilo, C(=O)-tienilo, fenilo o CH_2-(2,3,3-trimetil-ciclopent-1-enilo).

Otros compuestos preferidos de la fórmula (I) son aquellos en los cuales

- R_1 es:

alquilo de C_4-C_6,

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo bicíclico,

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace, un heterociclo divalente o un alquileno inferior, y
- R_4 se selecciona de:

1) H, =O, halógeno, CN, haloalquilo inferior, preferentemente CF_3, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=S)NR_9R_{10}$.

Otros compuestos preferidos de la fórmula (I) son aquellos en donde R_2 es alquilo inferior.

Otros compuestos preferidos de la fórmula (I) son aquellos donde R_3 es X_2-R'_3 en donde,

- X_2 es un solo enlace, alquileno de C_1-C_4, alquenileno de C_2-C_6 o alquinileno de C_2-C_6 y

- R'3 es:

  cicloalquilo,

  cicloalquenilo,

  arilo,

  heterociclo,

  o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace, o alquileno inferior, y
- R_{17} es:

  1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

  4) heterociclo optativamente sustituido con uno o varios grupos R_5.

Compuestos particularmente preferidos de la fórmula (I) son aquellos en donde R_1 es:

cicloalquilo, preferentemente ciclohexano,

cicloalquenilo,

arilo, preferentemente fenilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace o un heterociclo divalente, y,

- R_4 se selecciona de:

1) H, halógeno, CF_3, =O,

2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$.

Otros compuestos particularmente preferidos de la fórmula (I) son aquellos en donde R_2 es CH_3.

Otros compuestos particularmente preferidos de la fórmula (I) son aquellos en donde R_3 es X_2-R'_3 en donde,

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6, y

- R'_3 es:

cicloalquilo,

arilo, preferentemente fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17} idénticos o diferentes, en donde:

- X_3 es un solo enlace o $-CH_2-$, y,

- R_{17} es:

1) H, CN, CF_3, halógeno, NO_2,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=N-CN)NR_9R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

Compuestos más preferidos de la fórmula (I) son aquellos en donde

- R_1 es:

  alquilo de C_4-C_6,

  cicloalquilo,

  cicloalquenilo,

  heterociclo,

  arilo,

  o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es a un solo enlace, un heterociclo divalente o un alquileno inferior, y
- R_4 se selecciona de:

1) H, =O, halógeno, CN, haloalquilo inferior, preferentemente CF_3, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=S)NR_9R_{10}$,

R_2 es alquilo inferior, y,

R_3 es X_2-R'_3 en donde,

- X_2 es un solo enlace, alquileno de C_1-C_4, alquenileno de C_2-C_6 o alquinileno de C_2-C_6 y,
- R'_3 es:

  cicloalquilo,

  cicloalquenilo

  arilo,

  heterociclo,

  o un grupo policíclico,

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o alquileno inferior, y
- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se

seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con grupos R_5.

Otros compuestos más preferidos de la fórmula (I) son aquellos en donde

R_1 es:

cicloalquilo, preferentemente ciclohexano,

cicloalquenilo,

arilo, preferentemente fenilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace o un heterociclo divalente, y
- R_4 se selecciona de:

1) H, halógeno, CF_3, =O,

2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$,

R_2 es CH_3, y,

R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6,

y

- R'_3 es:

  cicloalquilo,

  arilo, preferentemente fenilo,

  heterociclo,

  o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o $-CH_2-$, y

- R_{17} es:

1) H, CN, CF_3, halógeno, NO_2

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=N-CN)NR_9R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

Otros compuestos más preferidos de la fórmula (I) son aquellos en donde

Y es O,

R_1 es:

cicloalquilo, preferentemente ciclohexano,

cicloalquenilo,

arilo, preferentemente fenilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace o un heterociclo divalente, y
- R_4 se selecciona de:

1) H, halógeno, CF_3, =O,

2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$,

R_2 es CH_3, y

R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6, y
- R'_3 es:

cicloalquilo,

arilo, preferentemente fenilo,

heterociclo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o $-CH_2-$, y

- R_{17} es:

  1) H, CN, CF_3, halógeno, NO_2

  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=N-CN)NR_9R_{10}$,

  4) heterociclo optativamente sustituido con uno o varios grupos R_5.

Más específicamente, un grupo de los compuestos de la fórmula (I) que se ha hallado que es de particular interés son aquellos en donde:

ciclohexano,

fenilo

o un grupo bicíclico

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace o un heterociclo divalente, y
- R_4 se selecciona de:

  1) H, halógeno, CF_3,

  2) COOH, OH,

  3) $C(=O)NR_7R_8$ en donde R_7 y R_8 son iguales o diferentes y se seleccionan de H o alquilo inferior;

R_2 es CH_3, y

R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6, y
- R'_3 es:

  fenilo,

  heterociclo,

  o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace, y
- R_{17} es:

  1) CN, OH, CF_3, =O, C_1-C_6 alcoxi, halógeno,

  2) $COOR_5$, SO_2R_5,

  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 o R_6,

  4) heterociclo optativamente sustituido con uno o varios grupos R_5.

Los compuestos más preferidos de la fórmula (I) son aquellos en donde Y es S.

Preferentemente, en cada una de las definiciones precedentes de R_1:

- R_5 se selecciona de

- H, o,
- alquilo inferior, optativamente sustituido con OH, preferentemente CH_3.

- R_6 se selecciona de
  - H, o,
  - alquilo inferior, preferentemente CH_3.
- R_9 y R_{10} se seleccionan de
  - H, o,
  - alquilo inferior, preferentemente CH_3.

Preferentemente, en cada una de las definiciones precedentes de R_2:

- R_5 y R_6 se seleccionan de
  - H, o,
  - alquilo inferior, preferentemente CH_3.
- R_9 y R_{10} se seleccionan de:
  - H, o,
  - alquilo inferior, preferentemente CH_3.

Los compuestos preferidos son:

I1 Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I1.1 Ácido (1R*, 2R*)-2-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico

I1.2 (S)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fenil-etanol

I1.7 2-{2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-etanol

I1.9 {1-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclopentil}-metanol

I1,10 Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico

I2.1 Ácido 5-[5-(4-cloro-fenil)-3-metil-3H[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico

I2.2 Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2,5,6-trifluoro-benzoico

I3 [5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-propil-amina

I3.1 (S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol

I3.3 [5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclobutil-amina

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I3.4 3-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-azepan-2-ona

I3.7 [5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclopentil-amina

I3.8 [5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-cicloheptil-amina

I3.10 (S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-3-metil-butan-1-ol

I3.11 2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-metil-propan-1-ol

I3.13 terc-Butil-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I3.14 [5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-isopropil-amina

I3.15 Ácido 4-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I3.16 [5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(1-etil-propil)-amina

I3.17 4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol

I3.18 N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,2-diamina

I3.19 [5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-fluoro-fenil)-amina

I3.20 N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,4-diamina

I3.25 (1R*, 2S*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol

I3.26 [5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-trifluorometil-fenil)-amina

I4 Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I5 3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol

I6 Ácido 5-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico

I6.1 (1-Aza-biciclo[2.2.2]oct-3-il)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I6.3 2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol

I6.5 (R)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol

I6.7 [5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-fluoro-fenil)-amina

I6.8 (3-Cloro-fenil)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I6.9 Ácido {3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-acético

I6.11 3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzamida

I7 Biciclo[2.2.1]hept-2-il-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-amina

I8 (1R*, 2R*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol

I8.1 5-(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-2-metoxi-fenol

I8.2 Ácido 3-(5-ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-benzoico

I8.3 Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-4-hidroxi-benzoico

I8.4 (5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-(3-metanosulfonil-fenil)-amina

I9 (1R*, 2R*)-2-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol

I10 Ciclohexil-[5-(2,4-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I10.1 [5-(2-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I11 Ciclohexil-[3-metil-5-(4-trifluorometil-fenil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina

I12 Ciclohexil-(3-metil-5-piridin-4-il-3H-[1,3,4]tiadiazol-2-iliden)-amina

I13 [5-(3-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I14 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo

I15 Ciclohexil-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I15.1 [3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina

I15.2 Ciclohexil-[5-(3-metoxi-4-nitro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I16 2,4-Dicloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida

I17 Ciclohexil-(3-metil-5-tiofen-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina

I17.1 Ciclohexil-[5-(3,5-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I17.2 Ciclohexil-[5-(2-etil-5-metil-2H-pirazol-3-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I18 [5-(3-Cloro-2,6-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I18.1 Ciclohexil-(5-isoxazol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-amina

I18.2 Ciclohexil-[3-metil-5-(5-piridin-2-il-tiofen-2-il)-3H-[1,3,4]tiadiazol-2-iliden]-amina

I18.3 5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico

I18.4 5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico

I18.5 [5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I18.6 2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-6-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico

I19 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida

I19.1 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida

I19.2 {5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina

I19.3 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida

I19.4 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida

I19.5 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida

I19.6 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida

I19.7 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida

I19.8 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida

I19.9 C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida

I19.10 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida

I19.11 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida

I19.12 2-Cloro-5-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dietilamino-etil)-N-etil-bencenosulfonamida

I19.14 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-propil)-N-etil-bencenosulfonamida

I20 Metil éster del ácido [5-(4-Cloro-fenil)-2-ciclohexilimino-[1,3,4]tiadiazol-3-il]-acético

I21 Metil éster del ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

I21.1 Ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

I21.2 3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

I21.3 3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-hidroxi-etil)-benzamida

I21.4 3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida

I22 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2-diol

I23 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,6-dimetoxi-fenol

I23.1 6-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-piridin-2-ol

I23.2 5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2,3-triol

I24 2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinolin-8-ol

I25 Ciclohexil-(3-metil-5-pirazin-2-il-3H-[1,3,4]tiadiazol-2-iliden)-amina

I26 5-[(E)-2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-vinil]-2-metoxi-fenol

I27 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol

I28 Ciclohexil-(3-metil-5-quinolin-8-il-3H-[1,3,4]tiadiazol-2-iliden)-amina

I29 [4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina

I30 4-(5-Ciclohexilimino-4-methyl-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida

I31 [5-(5-Cloro-1H-indol-2-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina; compuesto con ácido trifluoro-metanesulfónico

I31.1 Ácido 2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico

I32 5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico

I33 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico

I34 Ciclohexil-[5-(3,4-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I35 [5-(3-Bromo-4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I35.1 Ciclohexil-[5-(4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

I35.2 Ciclohexil-(3-metil-5-fenil-3H-[1,3,4]tiadiazol-2-iliden)-amina

I36 3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol

I37 Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

I37.1 Ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

I37.2 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-hidroxi-benzamida

I37.3 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

I37.4 Sal de clorhidrato de 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-*N*-(2H-tetrazol-5-il)-benzamida

I37.5 4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida

I37.6 4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida

I37.7 4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida

I37.8 4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida

I37.8-1 Ciclohexil-{5-[4-(1-etil-1H-tetrazol-5-il)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-amina

I37.9 4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida

I37.10 4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida

I37.11 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida

I37.12 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isobutil-benzamida

I37.13 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida

I37.13-1 4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-N-metil-benzamida

I37.14 [4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-1-(3-hidroximetil-piperidin-1-il)-metanona

I37.15 terc-Butil éster del ácido 2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico

I37.15-a Ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico; compuesto con ácido 2,2,2-trifluoro-acético

I37.16 terc-Butil éster del ácido (S)-2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-propiónico

I37.16-a Ácido (S)-2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-benzoilamino]-propiónico; compuesto con ácido 2,2,2-trifluoro-acético

I37.17 [4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-piridin-2-il-piperazin-1-il)-metanona

I37.18 [4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-[4-(4-fluoro-fenil)-piperazin-1-il]-metanona

I37.19 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida

I37.20 [4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-pirimidin-2-il-piperazin-1-il)-metanona,

I37.21 [4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-metil-piperazin-1-il)-metanona

I37.22 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida

I37.23 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(1-etil-pirrolidin-2-ilmetil)-benzamida

I37.24 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida

I37.25 N-Bencil-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

I37.26 N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

I37.27 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-l)-benzamida

I37.28 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida

I37.28-1 [5-(4-((N-ciano-N'-etilmorfolin)-carboximidamido)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I37.29 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida

I38 Ciclohexil-(3-metil-5-piridin-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina

I39 3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida

I40 (5-Benzo[1,3]dioxol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-ciclohexil-amina

I41 Ciclohexil-[3-metil-5-(3,4,5-trimetoxi-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina

I42 4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo

I43 4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo

I44 4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I45 4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I46 Ácido 5-[5-(4-Ciano-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico

I47-a 4-[4-Metil-5-(cis-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I47-b 4-[4-Metil-5-(trans-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I48 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I49 4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I50 4-[5-((1R*, 2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I51 4-[5-((1R*, 2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I52-a 4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I52-b 4-[5-((1R*, 3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I53 (1R*, 3R*))-3-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol

I54 Ácido 4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il}-benzoico

I55 4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-morfolin-4-il-etil)-benzamida

I56 Ácido 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico

I57 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida

I58 4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida

I59 N-terc-Butil-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I60 N-(1,1-dimetil-3-oxo-butil)-4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I61 N-(2-Ciano-1,2,2-trimetil-etil)-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I62 Metil éster del ácido 1-{4-[5-((1R*,3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoilamino}-ciclopropanocarboxílico

I63 4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-benzamida

I64 4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

I65 4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I66 4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I67 Ácido 5-[5-(4-Carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico

I68 4-[4-Metil-5-(4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I69 4-[5-(4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I70 4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I71 4-[5-((1R*,2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I72 4-[5-((1R*,2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I73 4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I74 4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I74.1 4-[4-Metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I75 4-[5-(3,3-Difluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I76 4-[5-((1R*,3R*)-3-Fluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I77 4-[5-(Ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

I78 (1R*,3R*)-3-{3-Metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-ilidenamino}-ciclohexanol

I79 Ácido 3-[5-(4-cloro-fenyl)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico

I80 Ácido 3-[5-(4-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I80.1 Ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I81 Ácido 2-fluoro-5-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I82 Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico

I83 [5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-piperidin-1-il amina

I84 [5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(tetrahidro-piran-4-il)-amina

I85 Ácido 3-[5-(4-acetilamino-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I86 N-{4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida

I87 N-{4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida

I88 N-{4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida

I89 *N*-{5-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-piridin-2-il}-acetamida

I90 3-[5-(4-Cloro-fenil)-3-metil-3H/-[1,3,4]tiadiazol-2-ilidenamino]-benzonitrilo

I90.1 [5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina

I90.2 3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-N-hidroxi-benzamidina

I90.3 3-{3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-[1,2,4]oxadiazol-5-ol

I91 [5-(4-Bromo-3-metil-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I91.1 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzonitrilo

I91.2 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzamida

I92 [5-(4-Bromo-3-metoxi-fenil)-3-metil-2,3-dihidro-[1,3,4]tiadiazol-2-il]-ciclohexil-amina

I92.1 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-benzamida

I92.2 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-hidroxi-benzamida

I93 Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-nitro-benzoico

I93.1 Metil éster del ácido 2-amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

I93.2 Metil éster del ácido 2-acetilamino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

I93.3 2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

I93.4 7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona

I93.5 7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina

I93.6 7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-1H-quinazolin-2,4-diona

I94 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida

I95 5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida

I96 Metil éster del ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I96.1 Ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I97.1 Ácido 3-[3-metil-5-piridin-2-il-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I98 Ácido 3-[5-(4-Cloro-3-sulfamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I99 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo

I99.1 Ciclohexil-{3-metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-iliden}-amina

I100 Ciclohexil-[3-metil-5-(4-nitro-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina

I100.1 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenilamina

I100.2 [5-(4-(N-ciano-N'-(2-dimetilaminoetil)-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I100.3 N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida

I100.4 [5-(4-(bis-etilsulfonilamino)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I100.5 [5-(4-(1-(2-dimetilaminoetil)amino-2-nitro-vinilamino)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I100.6 (E)-N^1-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-2-nitro-eten-1,1-diamina

I100.7 [5-(*N*-ciano-*N'*-metil-4-carboximidamido-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I100.8 [5-(4-(N-ciano-N'-amino-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I100.9 [4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-amida del ácido etanosulfónico

I100.10 [4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-urea

I100.11 1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea

I101 2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida

I102 Metil éster del ácido 2-cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

I102.1 2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

I103 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

I104 Metil éster del ácido 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzoico

I104.1 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzamida

Los compuestos utilizados en la invención incluyen derivados farmacéuticamente aceptables de los compuestos de la fórmula

(I) tales como solvatos, hidratos, sales farmacéuticamente aceptables y polimorfos (diferentes descriptores reticulados cristalinos).

Las sales farmacéuticamente aceptables de un compuesto de la fórmula (I) incluyen sales que tienen una parte básica y sales que tienen una parte ácida.

La expresión sal farmacéuticamente aceptable de un compuesto de la fórmula (I) que tiene una parte básica se refiere a las sales de adición de los compuestos de la fórmula (I) que se pueden formar desde ácidos inorgánicos u orgánicos no tóxicos tales como, por ejemplo, sales de ácido bromhídrico, clorhídrico, sulfúrico, fosfórico, nítrico, acético, succínico, tartárico, cítrico, maleico, hidroximaleico, benzoico, fumárico, toluenosulfónico e isetiónico, y similares. Las diversas sales de amonio cuaternario de los derivados (I) también están incluidas en esta categoría de compuestos de la invención. Además, la expresión sal farmacéuticamente aceptable de un compuesto de la fórmula (I) que tiene una parte ácida se refiere a las sales habituales de los compuestos de la fórmula (I) que pueden formarse desde bases inorgánicas u orgánicas no tóxicas tales como, por ejemplo, los hidróxidos de metales alcalinos y metales alcalinotérreos (sodio, potasio, magnesio y calcio), aminas

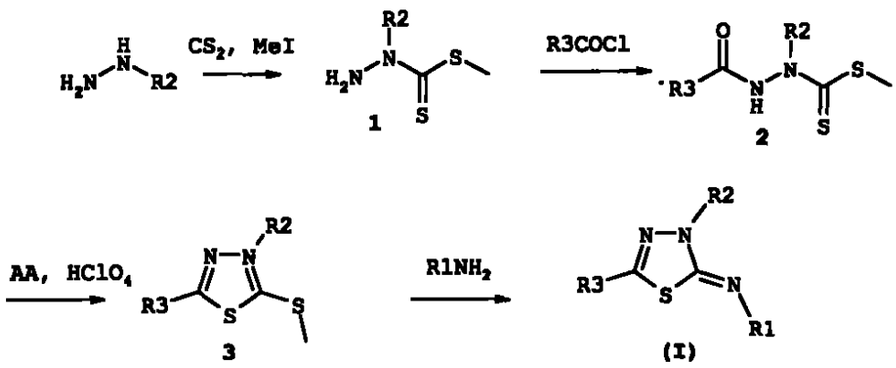
(dibenciletilendiamina, trimetilamina, piperidina, pirrolidina, bencilamina y similares) o alternativamente hidróxidos de amonio cuaternario tales como hidróxido de tetrametilamonio. (Ver también "Sales Farmacéuticas" de Berge S.M. et al. (1997) J. Pharm. Sci. 66: 1-19, que se incorpora aquí como referencia).

También se contempla el uso de una prodroga de un compuesto de la invención tal como el que se le puede ocurrir a un experto en el arte (ver Bundgaard, *et al.*, Acta Pharm. Suec., 1987; 24: 233-246).

Proceso para la preparación

Los compuestos de esta invención se pueden sintetizar de acuerdo con los procedimientos generales de síntesis A-E, utilizando la metodología descripta aquí que es conocida para un experto en el arte.

Protocolo A:



Lo compuestos iniciales están comercialmente disponibles o se pueden preparar de acuerdo con las vías conocidas para el hombre experto. Ver Akbar Ali, S.E. Livingston, y D.J. Philipps, *Inorganica Chimica Acta*, **6**, 11 (1972); P. Molina, A. Tarraga, A. Espinosa; *Synthesis*, **690** (1988); P. Molina, A. Tarraga, A. Espinosa; *Heterocycles*, vol.29, N°12 (1989).

En el paso 1, la hidrazina sustituida reacciona con disulfuro de carbono y con un yoduro de alquilo tal como yoduro de metilo para formar el S-alquilditiocarbazato 2-sustituido (1). Se pueden usar diversos solventes, condiciones de operación, bases, y pueden ser determinadas por la persona experta. Por ejemplo, sin ninguna limitación, se puede usar para la reacción de la hidrazina sustituida con un disulfuro de carbono, una solución alcohólica de hidróxido de potasio con una temperatura que no supere los 15°C. Se puede agregar

yoduro de metilo a esta solución o a una solución diluida (ej. con agua)..

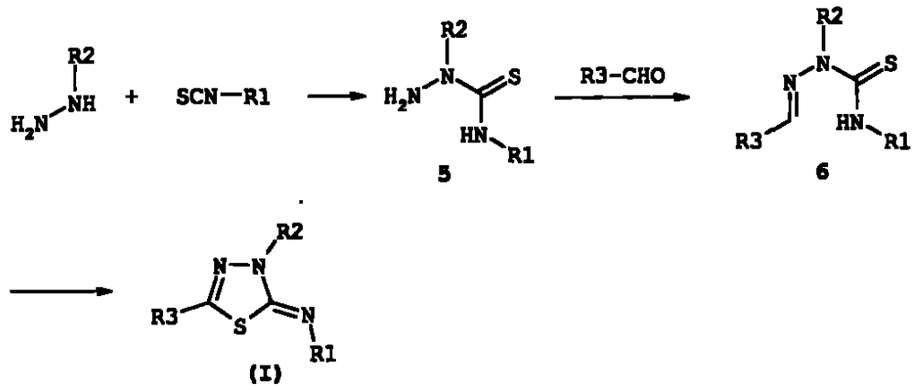
En el paso 2, el S-metiltiocarbazato sustituido reacciona con un grupo apropiado R_3CO-X en donde X es un grupo saliente tal como halógeno. Preferentemente, R_3CO-X es un cloruro de acilo (R_3COCl). La reacción se puede llevar a cabo en ej. tolueno como el solvente a reflujo. Se obtiene el metilditiocarbazato acilado (2) correspondiente.

En el paso 3, el metilditiocarbazato acilado es ciclado en el 1,3,4-tiadiazol deseado. La reacción se puede llevar a cabo en presencia de anhídrido acético (AA) y perclorato $HclO_4$ en éter, preferentemente, a una temperatura comprendida entre -5°C y 5°C, o en presencia de trimetilsilil trifluorometanosulfonato en diclorometano, preferentemente, a una temperatura comprendida entre 0°C y 25°C. Después de agitar a temperatura ambiente varias horas, se obtiene un compuesto intermedio que es el perclorato de 1,3,4-tiadiazolio (3).

En el paso 4, el 1,3,4-tiadiazol (o su perclorato o sulfonato) reacciona con una amina adecuada R_1NH_2, para formar el compuesto final. La reacción se puede llevar a cabo en alcohol tal como etanol como solvente (el solvente también puede ser un solvente aprótico tal como dioxano, dimetilformamida (DMF)

o acetonitrilo), en presencia de una base tal como trietilamina, y preferentemente, a una temperatura comprendida entre 40°C y 110°C, preferentemente entre 40°C y 80°C.

Protocolo B:



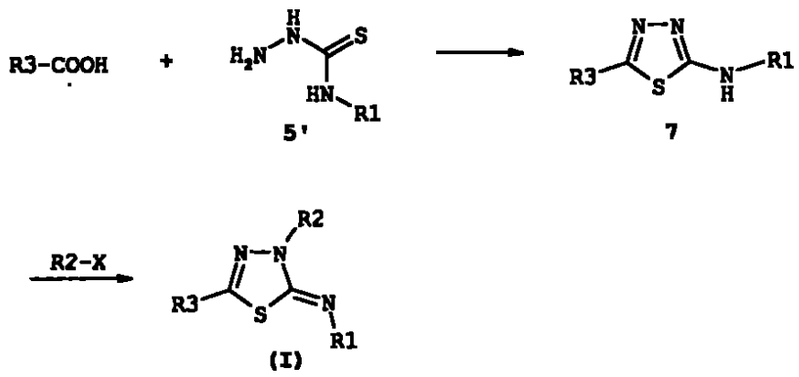
Los compuestos iniciales están comercialmente disponibles o se pueden preparar de acuerdo con las vías conocidas para la persona experta. Ver R. Noto, P. Lo Meo, M. Gruttadauria, G. Werber; *J. Heterocyclic Chem.*, 33, 863 (1996).

En el paso 1, el isotiocianato sustituido reacciona con la hidrazina sustituida para formar la tiosemicarbazida sustituida deseada (5). La reacción se puede llevar a cabo en alohol ej. metanol y/o agua a una temperatura comprendida entre -5°C y 15°C.

En el paso 2, la tiosemicarbazida sustituida reacciona con un aldehído R_3CHO para formar la tiosemicarbazona deseada (6). La reacción se puede llevar a cabo en alcohol, ej. metanol, a una temperatura comprendida entre 50°C y 90°C, preferentemente a 75°C.

En el paso 3, la tiosemicarbazona sustituida es ciclada para dar el compuesto (I). La reacción se puede llevar a cabo en alcohol, ej. etanol, a una temperatura comprendida entre 20°C y 110°C, preferentemente a 75°C, en presencia de un oxidante tal como $FeCl_3$.

Protocolo C:

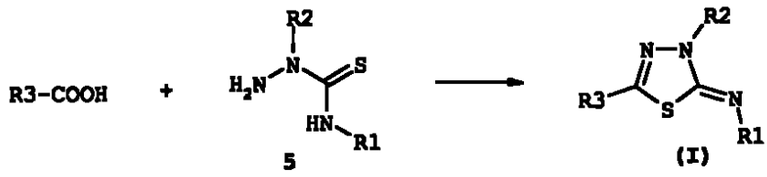


Los compuestos iniciales están comercialmente disponibles o se pueden preparar de acuerdo con las vías conocidas para la persona experta. Ver FR-A-712352, DE-A-4418066 y FR-A-8015072.

En el primer paso, el ácido carboxílico reacciona con el derivado de tiosemicarbazida (5') para dar el 1,3,4-tiadiazol deseado (7). La reacción se puede llevar a cabo en un solvente aprótico tal como dioxano, a reflujo, en presencia de un agente deshidratante, ej. $POCl_3$.

En el segundo paso, el 1,3,4-tiadiazol reacciona con R_2X, donde X es un grupo saliente tal como sulfonato, yoduro o bromuro de trifluorometano. La reacción se puede llevar a cabo en un solvente aprótico tal como dioxano o DMF (si R_2-X es yoduro o bromuro de alquilo), preferentemente a temperatura ambiente (RT) o con calentamiento para dar el compuesto (I).

Protocolo D: 1 paso



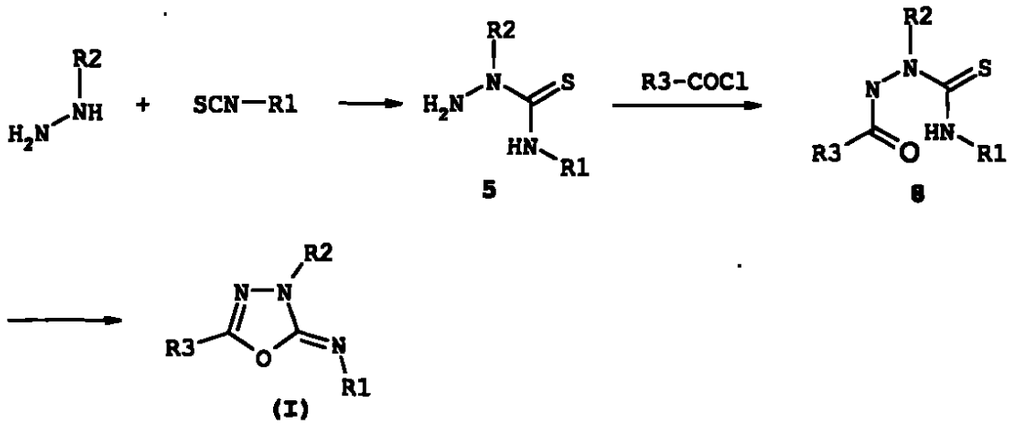
Los compuestos iniciales están comercialmente disponibles o se pueden preparar de acuerdo con las vías conocidas para el hombre experto.

En el primer paso, el ácido carboxílico reacciona con el derivado de tiosemicarbazida sustituida (5) para dar el 1,3,4-

tiadiazol final deseado (I). La reacción se puede llevar a cabo en un solvente aprótico tal como dioxano, a reflujo y a una temperatura comprendida entre 75°C y 120°C, en presencia de un agente deshidratante, ej. $POCl_3$.

El solvente, el tiempo de reacción, la temperatura, el catalizador si correspondiera, se pueden variar en todos los pasos descriptos anteriormente para todas las vías, según lo que aprecie el hombre experto.

Protocolo E: 3 pasos



Ver J.M. Kane, M.A. Staeger, Synthetic communication, 22 (1), 1-11 (1992).

Los compuestos iniciales están comercialmente disponibles o se pueden preparar de acuerdo con las vías conocidas para la

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persona experta. See R. Noto, P. Lo Meo, M. Gruttadauria, G. Werber; J. Heterocyclic Chem., 33, 863 (1996).

En el paso 1, el isotiocianato sustituido reacciona con la hidrazina sustituida para formar la tiosemicarbazida sustituida deseada (5). La reacción se puede llevar a cabo en un alcohol, ej. metanol y/o agua a una temperatura comprendida entre -5°C y 15°C, preferentemente 0°C.

En el paso 2, la tiosemicarbazida sustituida reacciona con el cloruro de ácido para formar la tiosemicarbazida deseada (8). La reacción se puede llevar a cabo en un medio básico tal como piridina a temperatura ambiente, o en un solvente aprótico en presencia de una base tal como piridina o trietilamina.

En el paso 3, la tiosemicarbazida sustituida es ciclada para dar el compuesto (I). La reacción se puede llevar a cabo en un alcohol, ej. metanol, a una temperatura de ej. 75°C, en presencia de óxido mercúrico (HgO).

Composiciones Farmacéuticas

Los productos de la invención se administran en forma de composiciones, que son apropiadas según la naturaleza, y la gravedad de la condición que se ha de tratar. La dosis diaria en

humanos es generalente entre 2 mg y 1 g del ingrediente activo, que se puede tomar en una o más dosis individuales. Las composiciones se preparan en formas que son compatibles con la vía de administración deseada, tal como, por ejemplo, tabletas, tabletas recubiertas, cápsulas, enjuagues bucales, aerosoles, polvos para inhalación, supositorios, enemas, espumas (tales como espumas rectales), geles o suspensiones. Estas composiciones se preparan mediante métodos que son conocidos para los conocedores del arte y comprenden del 0,5% al 60% en peso del ingrediente activo (el compuesto de la invención) y del 40% al 99,5% en peso de un vehículo o portador farmacéutico que es apropiado y compatible con el principio activo y la forma física de la composición deseada.

Las preparaciones en forma sólida incluyen polvos, tabletas, gránulos deseables, cápsulas y supositorios. Un portador sólido puede ser una o más sustancias que también pueden actuar como diluyentes, agentes saborizantes, solubilizadores, lubricantes, agentes de suspensión, ligantes, o agentes desintegradores de tabletas; también puede ser un material encapsulador. En los polvos, el portador es un sólido finamente dividido, que está en una mezcla con el componente activo finamente dividido. En las tabletas, el componente activo se mezcla con el portador que tiene las propiedades ligantes necesarias en proporciones adecuadas y se compacta en la forma y el tamaño deseados. Los

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polvos, tabletas, cápsulas o formas encapsuladas para cápsulas preferentemente contienen del 5% al 70% del componente activo. Los portadores adecuados son carbonato de magnesio, estearato de magnesio, talco, lactosa, azúcar, pectina, dextrina, almidón, tragacanto, metil celulosa, carboximetil celulosa de sodio, una cera con bajo punto de fusión, manteca de cacao y similares.

Las tabletas, polvos y cápsulas adecuadas se pueden usar como formas de dosificación sólidas adecuadas para la administración oral. La droga se puede administrar como una aspersión (en un recipiente presurizado equipado con una válvula apropiada o en un recipiente no presurizado equipado con una válvula medidora).

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones.

Las soluciones estériles en agua o agua-propilenglicol de los compuestos activos se pueden mencionar como un ejemplo de preparaciones líquidas adecuadas para la administración parenteral. Las preparaciones líquidas también se pueden formular en una solución acuosa de polietileno.

Las soluciones acuosas para la administración oral se pueden preparar disolviendo el componente activo en agua y agregando colorantes, agentes saborizantes, estabilizadores y agentes

espesantes adecuados según se desee. Las suspensiones acuosas para uso oral pueden hacerse dispersando el componente activo finamente dividido en agua junto con un material viscoso tal como gomas sintéticas, resinas, metil celulosa, carboximetil celulosa de sodio, y otros agentes de suspensión conocidos para el arte de las formulaciones farmacéuticas.

Para preparar supositorios, una cera de bajo punto de fusión tal como una mezcla de glicéridos de ácidos grasos y manteca de cacao se funde primero y el ingrediente activo se dispersa en ella mediante, por ejemplo agitación. La mezcla homogénea fundida luego se vierte en moldes convenientes y se la deja enfriar y solidificar. Los enemas se obtienen de acuerdo con procedimientos conocidos para preparar soluciones adaptadas para la administración rectal. Las espumas se preparan de acuerdo con métodos conocidos (estas espumas pueden ser notablemente similares a aquellas usadas para administrar una droga tal como 5-ASA para tratar rectocolita).

Preferentemente la preparación farmacéutica está en forma de dosificación unitaria. En esa forma, la preparación se divide en dosis unitarias que contienen cantidades apropiadas de la droga. La forma de dosificación unitaria puede ser una preparación envasada, el envase contiene cantidades discretas de la preparación, por ejemplo, tabletas, cápsulas, y polvos envasados

en frascos o ampollas. La forma de dosificación unitaria también puede ser una cápsula, o la cápsula misma, o puede ser el número apropiado de cualquiera de estas formas envasadas.

Métodos de tratamiento

Los compuestos de la invención son inhibidores selectivos de PDE7. Se pueden usar en el tratamiento de diversas enfermedades, ya que modulan procesos inflamatorios e inmunológicos debido a un aumento de los niveles intracelulares de cAMP.

Las enfermedades que se pueden tratar con éxito incluyen a saber enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas y exócrinas del páncreas, enfermedades gastrointestinales, dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

Los compuestos de la invención tienen bajos valores de IC50, típicamente como máximo 5 μM, preferentemente por debajo de 1 μM y aún debajo de 100 nM.

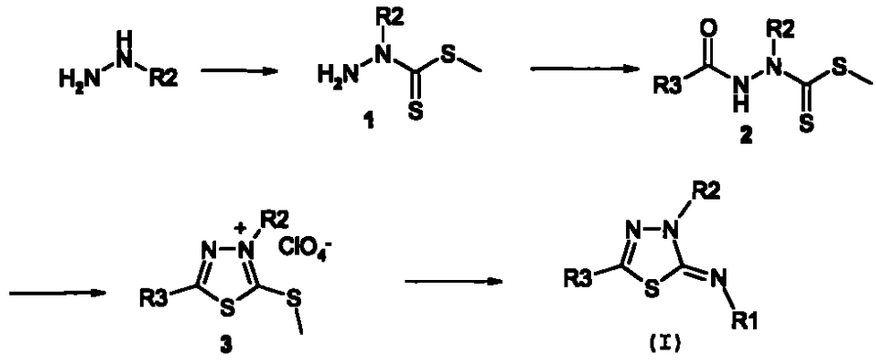
La invención finalmente se relaciona con un método para el tratamiento de las enfermedades mencionadas anteriormente que comprende administrar a un mamífero, particularmente un humano, que lo necesita, una cantidad efectiva de un compuesto de la invención.

Los siguientes ejemplos ilustran la invención sin limitarla.

Ejemplos

Los compuestos de la invención han sido nombrados con el software "AutoNom Versión 4.0".

Protocolo A:



Intermedio 1: PROTOCOLO A

Intermedio 1a: R_2= metilo

Metil éster del ácido N-metil-hidrazincarboditioico

Se agregó metilhidrazina (370 mmol, 19,43 mml) a una solución de hidróxido de potasio (370 mmol, 20,7 g) en alcohol acuoso al 90% (130 ml). La mezcla se enfrió a 5°C, luego se agregó disulfuro de carbono (370 mmol, 22,2 ml) gota a gota con agitación vigorosa, durante 1 h, mientras no se dejaba subir la temperatura de la mezcla por encima de 7°C. La solución amarilla resultante se diluyó con agua (300 ml) y el yoduro de metilo (370 mmol, 23,34 ml) se agregó lentamente mientras la mezcla se agitaba vigorosamente. Después de la agitación se hubo continuado durante 3 h a 10°C-15°C, los cristales blancos de 2-metil-S-metilditiocarbazato (1a) se filtraron, se lavaron con una mezcla de 1:1 de etanol:éter de petróleo para dar 38 g del compuesto deseado.

Rendimiento: 84%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 2,32 (s, 3H), 3,60 (s, 3H), 5,55 (s, 2H).

Intermedio 2: PROTOCOLO A

Intermedio 2a: R_2= metilo, R_3= 4-cloro-fenilo

Metil éster del ácido N'-[1-(4-Cloro-fenil)-metanoil]-N-metil-hidrazincarboditioico

El cloruro de acilo apropiado (73,39 mmol, 9,30 ml) (R_3COCl) se agregó a una suspensión de 2-metil-S-metilditiocarbazato (73,39 mmol, 10 g) en tolueno (80 ml). La mezcla se agitó a reflujo durante 4 h, luego se la dejó enfriar toda la noche. Los sólidos se aislaron mediante filtración, se lavaron con agua y luego con éter para dar 15 g del 3-acil-2-metil-S-metilditiocarbazato (**2a**) esperado.

Rendimiento= 74%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 2,45 (s, 3H), 3,65 (s, 3H), 7,65 (dd, 2H), 7,90 (dd, 2H), 11,68 (s, 1H).

Intermedio 2b: R_2= metilo, R_3= 4-(metilsulfonil)-fenilo

Metil éster del ácido N'-[1-(4-Metanosulfonil-fenil)-metanoil]-N-metil-hidrazincarboditioico

El cloruro de ácido se preparó desde el ácido benzoico correspondiente.

El cloruro de acilo apropiado (1,68 mmol, 0,39 g) se agregó a una suspensión de 2-metil-S-metilditiocarbazato (1,77 mmol, 0,24 g) en tolueno (2 ml). Después de 5 h a reflujo, la mezcla

se enfrió toda la noche, se trituró en éter y se agitó durante 2 h a RT para dar 440 mg del producto esperado (**2b**) como un sólido blanco.

Rendimiento= 82%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2,5 (s, 3H), 3,30 (s, 3H), 3,65 (s, 3H), 8,15 (m, 4H), 11,9 (s, 1H).

Intermedio 2c: R_2= metilo, R_3= 4-ciano-fenilo

Metil éster del ácido N'-[1-(4-Ciano-fenil)-metanoil]-N-metil-hidrazincarboditioico

El cloruro de acilo apropiado (22,77 mmol, 3,77 g) (R_3COCl) se agregó a una suspensión de 2-metil-S-metilditiocarbazato (22,77 mmol, 3,10 g) en tolueno (25 ml). La mezcla se agitó a reflujo durante 3h-3h30, luego se la dejó enfriar toda la noche. Los sólidos se aislaron por filtración, se lavaron con agua luego con éter y se secaron para dar 4,15 g del 3-acil-S-metilditiocarbazato esperado (2c).

Rendimiento= 68%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2,45 (s, 3H), 3,65 (s, 3H), 8,05 (m, 4H), 11,85 (s, 1H).

Intermedio 2d: R_2= metilo, R_3= 4-acetilamino-fenilo

Metil éster del ácido N'-(4-Acetilamino-benzoil)-N-metil-hidrazincarboditioico

El cloruro de ácido se preparó desde el ácido benzoico correspondiente.

A una suspensión del cloruro de acilo apropiado (10 mmol, 1,4 g) en tolueno (30 ml), se agregó trietilamina (20 mmol, 2,8 ml) seguido por 2-metil-S-metilditiocarbazato (12 mmol, 2,4 g). La mezcla se mantuvo a 90°C durante 2 horas y se concentró bajo presión reducida. El residuo se recogió en diclorometano, se lavó una vez con agua, se concentró bajo presión reducida y se lavó con AcOEt para dar 1,28 g del compuesto del título.

Rendimiento= 45%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 2,10 (s, 3H), 2,45 (s, 3H), 3,65 (s, 3H), 7,85 (d, 2H), 7,90 (d, 2H), 10,30 (s, 1H), 11,40 (s, 1H).

Intermedio 2e: R_2= metilo, R_3= 4-acetilamino-3-piridilo

Metil éster del ácido N'-(6-acetilamino-piridin-3-carbonil)-N-metil-hidrazincarboditioico

El cloruro de ácido se preparó desde el ácido benzoico correspondiente.

A una suspensión del cloruro de acilo apropiado (63 mmol, 11 g) en tolueno (150 ml) se agregó trietilamina (130 mmol)

seguida por 2-metil-S-metilditiocarbazato (62 mmol, 9 g). Después de 3 h a temperatura ambiente, la mezcla se concentró bajo presión reducida. El residuo se recogió en diclorometano, se lavó una vez con agua, se concentró bajo presión reducida y se purificó por cromatografía sobre gel de sílice (95:5 diclorometano (DMC)/MeOH) para dar 9 g del compuesto del título.

Rendimiento= 50%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 2,15 (s, 3H), 2,45 (s, 3H), 3,65 (s, 3H), 8,25 (m, 2H), 8,80 (s, 1H), 10,90 (s, 1H).

MS (m/z) / M+1= 298,99

Intermedio 3: PROTOCOLO A

Intermedio 3a: R_2= metilo, R_3= 4-cloro-fenilo

5-(5-clorofenil)-3-metil-2-(metiltio)-perclorato de 1,3,4-tiadiazolio

A una suspensión del (2a) (54,4 mmol, 15 g) en éter (150 ml) a 0°C, se agregó lentamente anhídrido acético (30 ml) y luego se agregó $HClO_4$ 70% (65,33 mmol, 5,61 ml) gota a gota a 0°C durante 1 hora. La mezcla resultante se agitó a RT toda la noche y el precipitado se separó por filtración, se lavó con éter y luego se secó al aire para dar 19 g del compuesto del título (3a) como un sólido blanco.

Rendimiento= 97%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 2,92 (s, 3H), 3,99 (s, 3H), 7,52 (dd, 2H), 7,82 (dd, 2H).

MS (m/z) / M+1 = 257/259

Intermedio 3b: R_2= metilo, R_3= 4-(metilsulfonil)fenilo

5-(4-Metanosulfonil-fenil)-3-metil-2-(metiltio)-perclorato de 1,3,4-tiadiazolio

A una suspensión del (2b) (0,69 mmol, 0,22 g) en éter (3 ml) a 0°C, se agregó lentamente anhídrido acético (0,4 ml) y luego se agregó $HClO_4$ 70% (0,90 mmol, 0,080 ml) gota a gota a 0°C durante 1 hora. Luego se dejó que la mezcla resultante aumentara a RT y se la agitó durante 3 h. El precipitado se aisló por filtración, luego se secó al aire para dar 220 mg del perclorato de 3-metil-2-metiltio[1,3,4]tiadiazolio (3b) esperado como un sólido blanco.

Rendimiento= 78%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,14 (s, 3H), 3,33 (s, 3H), 4,20 (s, 3H), 8,20 (dd, 2H), 8,25 (dd, 2H).

MS (m/z) / M+1 = 301/303

Intermedio 3c: R_2= metilo, R_3= 4-ciano-fenilo

5-(4-cianofenil)-3-metil-2-(metiltio)-percloratо de 1,3,4-tiadiazolio

A una suspensión del intermedio (2c) (15,64 mmol, 4,15 g) en éter (50 ml) y anhídrido acético (13,3 ml), se agregó $HClO_4$ 70% (18,76 mmol, 1,6 ml) gota a gota a 0°C y se agitó durante 15-30 minutos a 0°C. La mezcla resultante se agitó durante 1H30 a temperatura ambiente y el precipitado, separado por filtración, se lavó con éter y luego se secó al aire para dar 5,22 g del compuesto del título (3c) como un sólido blanco.

Rendimiento= 96%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,15 (s, 3H), 4,21 (s, 3H), 8,15 (m, 4H).

Intermedio 3d: R_2= metilo, R_3= 4-acetilamino-fenilo

Ácido 5-(4-acetilaminofenil)-3-metil-2-(metiltio)-trifluorometanosulfónico de 1,3,4-tiadiazolio

A una suspensión de (2d) (4,3 mmol, 1,28 g) en diclorometano (15 ml) se agregó trimetilsilil trifluorometano-sulfonato (12,9 mmol, 2,34 ml) gota a gota. La mezcla resultante se agitó toda la noche. El precipitado se aisló mediante filtración y luego se secó bajo presión reducida para dar 1,3 g del triflato de 3-metil-2-metiltio[1,3,4]tiadiazolio (3d) esperado como un sólido blanco.

Rendimiento= 72%

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^{1}H-NMR (400MHz, DMSO) δ ppm: 2,10 (s, 3H), 3,10 (s, 3H), 4,15 (s, 3H), 7,80 (dd, 2H), 7,95 (dd, 2H), 10,40 (s, 1H).

Intermedio 3e: R_2= metilo, R_3= 4-acetilamino-3-piridilo

5-(6-acetilamino-piridin-3-il)-3-metil-2-(metiltio)-perclorato de 1,3,4-tiadiazolio

A una suspensión de (2e) (3,4 mmol, 1 g) en éter (11 ml) se agregó lentamente anhídrido acético (2 ml) seguido por $HClO_4$ 70% (4 mmol, 0,7 g) gota a gota a 0°C durante 1 hora. La mezcla resultante luego se dejó calentar hasta la temperatura ambiente y se agitó toda la noche. Se agregó $HClO_4$ adicional (0,7 mmol, 0,1 g) a 0°C y la mezcla se agitó durante 2 h. El precipitado se aisló por filtración, se lavó con AcOEt, luego se secó bajo presión reducida para dar 1 g del (3e) esperado.

Rendimiento= 77%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2,15 (s, 3H), 3,15 (s, 3H), 4,20 (s, 3H), 8,30 (dd, 1H), 8,40 (dd, 2H), 8,90 (d, H), 11,05 (s, 1H).

MS (m/z) / M+1 = 280,92

Compuesto I: PROTOCOLO A

Ejemplo I1: R_1= ácido 3-benzoico, R_2= metilo, R_3= 4-cloro-fenilo

Ácido 3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

A una suspensión de perclorato de 1,3,4-tiadiazolio (**3a**) (0,7 mmol, 0,25 g) en etanol (3,5 ml), se agregaron ácido 3-aminobenzoico (1,05 mmol, 0,144 g) y trietilamina (0,7 mmol) y la mezcla se mantuvo a 70°C durante 7 horas. Al enfriar a RT toda la noche, el sólido formado se aisló por filtración para dar 0,180 g del compuesto esperado.

Rendimiento= 74,3%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,72 (s, 3H), 7,30 (dd, 1H), 7,5 (dd, 1H), 7,54 (dd, 2H), 7,60 (s, 1H), 7,54 (dd, 1H), 7,71 (dd, 2H), 12,91-13,04 (b, 1H).

MS (m/z) / M+1= 346/348

HPLC (pureza por uv, λ= 214 nm)= 99,03%

Los siguientes compuestos se prepararon mediante el procedimiento descripto en el ejemplo I.1 usando los intermedios y reactivos apropiados. Los productos deseados se obtuvieron después de la purificación por cromatografía sobre gel de sílice.

I1.1	ácido (1R*,2R*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico
I1.2	(S)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fenil-etanol
I1.3	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-etil-fenil)-amina
I1.4	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-pirrolidin-3-il-amina
I1.5	N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-N',N'-dimetil-bencen-1,4-diamina
I1.6	Ácido 2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-6-metil-benzoico
I1.7	2-{2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-etanol
I1.8	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-etil-fenil)-amina
I1.9	{1-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclopentil}-metanol

Ejemplo I1.10: R_1= ciclohexilo de ácido 3-carboxílico, R_2= metilo, R_3= 4-cloro-fenilo

Ácido 3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico

El compuesto I1.10 se preparó mediante el procedimiento descripto en el ejemplo I1 (3 h a 75°C) usando los intermedios y reactivos apropiados (protocolo A).

La mezcla se filtró y el filtrado se evaporó hasta secarse. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con diclorometano que contenía del 0% al 5% de metanol y luego elución isocrática con DCM/MeOH (90/10).

Rendimiento= 7,0%

^{1}H-NMR (400MHz, DMSO) δ ppm: 0,95-1,20 (m, 4H), 1,62-1,74 (m, 3H), 1,74-1,80 (m 1H), 2,10-2,13 (b, 1H), 2,39-2,48 (b, 1H), 2,84-2,90 (m, 1H), 3,10 (3H, s), 7,33 (dd, 2H), 7,44 (dd, 2H), 11,89-11,84 (b, 1H).

MS (m/z) / M+1 = 352/354

HPLC (pureza por uv, λ= 214 nm)= 97,61%

Ejemplo I2: R_1= ácido 2-benzoico, R_2= metilo, R_3 4-cloro-fenilo

Ácido 2-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

A una suspensión de perclorato de 1,3,4-tiadiazolio (**3a**) (0,7 mmol, 0,25 g) en etanol (3 ml), se agregaron ácido 2-aminobenzoico (0,84 mmol, 0,115 g) y trietilamina (0,7 mmol, 0,098 ml) y la mezcla se calentó a 70°C durante 7 horas. Al

enfriar, el sólido formado se filtró para dar 210 mg del compuesto esperado.

Rendimiento= 87%.

^{1}H-NMR (400MHz, DMSO)δ ppm: 3,8 (s, 3H), 7,20 (m, 1H), 7,28 (dd, 1H), 7,56-7,64 (m, 3H), 7,78 (dd, 2H), 7,95 (dd, 1H), 13,52-13,59 (b, 1H).

MS (m/z) / M+1= 346/348

HPLC (pureza uv, λ= 214 nm)= 97,64%

Ejemplo I2.1: R_1= ácido (4-fluoro)-3 benzoico, R_2= metilo, R_3= 4-cloro-fenilo

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico

El compuesto I2.1 se preparó mediante el procedimiento descripto en el ejemplo I2 usando los intermedios y reactivos apropiados (protocolo A).

El precipitado obtenido al enfriar se lavó con EtOH para dar 0,250 g del compuesto del título.

Rendimiento= 60%

^{1}H-NMR (400MHz, DMSO) δ pm: 3,71 (s, 3H), 7,29-7,33 (m, 3H), 7,48-7,51 (m 1H), 7,54 (dd, 2H), 7,70 (dd, 2H), 13,27-13,29 (b, 1H).

MS (m/z) / M+1= 364/366

HPLC (pureza uv, λ= 214 nm)= 95,77%

Ejemplo I2.2: R_1= ácido (2,4,5-fluoro)-3 benzoico, R_2= metilo, R_3= 4-cloro-fenilo

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2,5,6-trifluoro-benzoico

El compuesto I2.2 se preparó mediante el procedimiento descripto en el ejemplo I2 usando los intermedios y reactivos apropiados. Se usó acetonitrilo como solvente y la reacción se calentó a 80°C durante 24 h (protocolo A).

El sólido formado después de enfriar se filtró y se lavó con MeOH para dar 0,250 g del compuesto del título.

Rendimiento= 48,6%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,74 (s, 3H), 7,44-7,54 (m, 1H), 7,55 (dd, 2H), 7,73 (dd, 2H), 14,15-14,30 (b, 1H).

MS (m/z) / M+1= 400/402

HPLC (pureza uv, λ= 214 nm)= 95,82%

Ejemplo I3: R_1= propilo, R_2= metilo, R_3= 4-cloro-fenilo

[5-(5-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-propil-amina

A una suspensión de perclorato de 1,3,4-tiadiazolio (**3a**) (0,28 mmol, 0,10 g) en metanol (4 ml), se agregaron propilamina (1,35 mmol, 0,115 ml) y trietilamina (0,28 mmol, 0,038 ml) y la reacción se calentó a 55°C durante 5 horas. Al enfriar, la mezcla se evaporó hasta secarse y el compuesto crudo se cromatografió sobre gel de sílice (columna de Alltech, 2 g de sílice) con una mezcla de ciclohexano:EtOAc (98:2) para dar el compuesto esperado.

Rendimiento= 0,03 g, 45,2%.

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,89 (t, 3H), 5,53-5,65 (m, 2H), 2,97 (t, 2H), 7,49 (dd, 2H), 7,62 (dd, 2H).

MS (m/z) / M+1= 268/270

HPLC (pureza uv, λ= 214 nm)= 97,60%

Los siguientes compuestos se prepararon mediante el procedimiento descripto en el ejemplo **I3** usando los intermedios y reactivos apropiados.

I3.1	(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol
I3.2	[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-[3-(4-metil-piperazin-1-il)-propil]-amina
I3.3	[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclobutil-amina

I3.4	3-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-azepan-2-ona
I3.5	(4-Cloro-bencil)-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-amina
I3.6	Bencil-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-amina
I3.7	[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclopentil-amina
I3.8	[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-cicloheptil-amina
I3.9	(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-3-fenil-propan-1-ol
I3.10	(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-3-metil-butan-1-ol

Los siguientes compuestos se prepararon mediante el procedimiento descripto en el ejemplo I3 usando los intermedios y reactivos apropiados y con isopropanol como solvente.

I3.11	2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-metil-propan-1-ol
I3.12	2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroximetil-propano-1,3-diol

I3.13	terc-Butil-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina
I3.14	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-isopropil-amina
I3.15	ácido 4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico
I3.16	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(1-etil-propil)-amina
I3.17	4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol
I3.18	N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,2-diamina
I3.19	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-fluoro-fenil)-amina
I3.20	N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,4-diamina
I3.21	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3,4-dicloro-fenil)-amina
I3.22	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-metoxi-fenil)-amina
I3.23	ácido (1R*,2S*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico
I3.24	N'-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-

	iliden]-N,N-dimetil-etano-1,2-diamina

Ejemplo I3.25: R_1= (1R*,2S*)-ciclohexil-2-ol, R_2= metilo, R_3= 4-cloro-fenilo

(1R*,2S*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol

El compuesto I3.25 se preparó mediante el procedimiento descripto en el ejemplo I3 (protocolo A) con isopropanol como solvente.

El producto del título se aisló por cromatografía sobre gel de sílice (Alltech, 2 g de sílice) eluyendo con diclorometano que contenía del 0% al 1% de metanol.

Rendimiento= 0,015 g, 12%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,30 (b, 2H), 1,40-1,50 (b, 2H), 1,50-1,72 (b, 4H), 2,80-2,83 (b, 1H), 3,50 (s, 3H), 3,55-3,60 (b, 1H), 4,02-4,04 (b, 1H), 7,45 (d, 2H), 7,60 (d, 2H).

MS (m/z) / M+1= 324/3256

HPLC (uv purity, λ = 214 nm)= 96,62%

El siguiente compuesto se preparó mediante el procedimiento descripto en el ejemplo I3 con isopropanol como solvente.

I3.26	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-trifluorometil-fenil)-amina

Ejemplo I4: R_1= ácido 3-benzoico, R_2= metilo, R_3= 4-(metanosulfonil)-fenilo

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

A una suspensión de perclorato de 1,3,4-tiadiazolio (**3b**) (0,547 mmol, 0,22 g) en etanol (2,5 ml), se agregó ácido 3-aminobenzoico (0,547 mmol, 0,075 g) y trietilamina (0,601 mmol, 0,084 ml), y la reacción se mantuvo durante 6 horas a 75°C. Después de enfriar toda la noche, el precipitado se filtró, se lavó con etanol, luego se purificó sobre gel de sílice, se eluyó con un gradiente de DCM luego DCM:MeOH (95:5) para dar 70 mg del compuesto esperado.

Rendimiento= 33%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,78 (s, 3H), 7,31 (dd, 1H), 7,54 (dd, 1H), 7,60 (s, 1H), 7,65 (s, 1H), 7,97 (dd, 2H), 8,03 (dd, 2H), 12,92-12,03 (b, 1H).

MS (m/z) / M+1= 390

HPLC (pureza uv, λ= 214 nm)= 95,14%

Los siguientes compuestos se prepararon mediante el procedimiento descripto en el ejemplo I4 con un exceso de trietilamina (10 eq) y de la amina apropiada (10 eq). La reacción se refluyó durante 5 h.

I4.1	[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclopropil-amina
I4.2	[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexilmetil-amina

Ejemplo I5: R_1= 3-hidroxifenilo, R_2= metilo, R_3= 4-clorofenilo

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol

En este ejemplo, se usó resina de morfolina de poliestireno para reemplazar la trietilamina y la resina de isocianato para remover el derivado de amino restante.

La suspensión de resina de morfolina (0,70 mmol, 0,20 g) 3-aminofenol (0,84 mmol, 0,09 g) en etanol (3,5 ml) se agitó a RT durante 5 minutos antes del agregado de perclorato de 1,3,4-tiadiazolio (**3a**) (0,70 mmol, 0,25 g). Después de 5 horas a 70°C, se dejó enfriar la mezcla antes de la filtración de la resina. El compuesto crudo obtenido después de la evaporación del solvente se purificó sobre gel de cromatografía (columna

de Alltech, 2 g de sílice) y se eluyó con un gradiente de DCM y MeOH:DCM (99:1) para dar una mezcla (0,07 g) del derivado de amino restante y el compuesto esperado. A esta mezcla en DCM (7 ml) / MeOH (0,5 ml), se agregó la resina de isocianato (2,44 mmol, 2,00 g) y la suspensión se agitó a RT toda la noche. Después de la filtración de la resina, el filtrado se evaporó hasta secarse para dar 30 mg del producto puro.

Rendimiento= 13,5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,68 (s, 3H), 6,45-6,51 (m, 3H), 7,13-7,19 (m, 1H), 7,55 (dd, 2H), 7,71 (dd, 2H), 9,40-9,48 (b, 1H).

MS (m/z) / M+1= 318/320

HPLC (pureza uv, λ = 214 nm)= 98,44%

Ejemplo I6: R_1= ácido 4-hidroxi-3-benzoico, R_2= metilo, R_3= 4-clorofenilo

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico

El compuesto I6 se preparó mediante el procedimiento descripto en el ejemplo I2 (protocolo A). El precipitado obtenido después de enfriar se lavó con DCM luego se purificó por cromatografía sobre gel de sílice (columna de Alltech, 5 g de sílice) se eluyó con una mezcla de DCM/MeOH de 100/0 a 85/15.

Rendimiento= 17,0%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,07 (s, 1H), 3,59 (s, 3H), 6,70 (d, 1H), 6,93-6,98 (m 1H), 7,30 (s, 1H), 7,38-7.41 (m, 2H), 7,57-7,62 (m, 2H).

MS (m/z) / M+1= 362/364

HPLC (pureza uv, λ= 214 nm)= 95,89%

Los siguientes compuestos se prepararon mediante el procedimiento descripto en el ejemplo I6, usando los intermedios y reactivos apropiados. Se usó resina de morfolina o piridina para reemplazar la trietilamina.

I6.1	(1-Aza-biciclo[2.2.2]oct-3-il)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina
I6.2	4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-dietilaminometil-fenol
I6.3	2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol
I6.4	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(2-etil-fenil)-amina
I6.5	(R)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol
I6.6	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-metoxi-fenil)-amina

I6.7	[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-fluoro-fenil)-amina
I6.8	(3-Cloro-fenil)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina
I6.9	ácido {3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-acético
I6.10	N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-N',N'-dimetil-bencen-1,3-diamina
I6.11	3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzamida

Ejemplo I7: R_1= exo-2-norbornilo, R_2= metilo, R_3= 4-cloro-fenilo

Biciclo[2.2.1]hept-2-il-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

El compuesto I7 se preparó mediante el procedimiento descripto en el ejemplo I3 usando los intermedios y reactivos apropiados (protorolo A).

El producto del título se aisló mediante cromatografía sobre gel de sílice (Alltech, 2g de sílice) con un gradiente de ciclohexano: EtOAc de 100:0 a 97:3

Rendimiento= 44,8%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,09-1,18 (b, 3H), 1,27-1,33 (b, 1H), 1,40-1,52 (b, 2H), 1,58-1,62 (m, 1H), 1,70-1,76 (m, 1H), 1,99-2,10 (b, 1H), 2,24-2,27 (b, 1H), 3,45 (s, 3H), 7,53 (d, 2H) 7,64 (d, 2H).

MS (m/z) / M+1= 320/322

HPLC (pureza uv, λ= 214 nm)= 93,17%

Ejemplo I8: R_1= (1R*,2R*)-ciclohexil-2-ol, R_2= metilo, R_3= 4-cloro-fenilo

(1R*,2R*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol

El compuesto I8 se preparó mediante el procedimiento descripto en el ejemplo I3 usando los intermedios y reactivos apropiados (protocolo A).

La trietilamina se reemplazó por resina de morfolina (2,1 mmol, 0,61 g, cargando 3,47 mmol/g); la mezcla de resina de morfolina y clorhidrato de trans-2-aminociclohexanol (2,1 mmol, 0,318 g) se agitó en etanol (3,5 ml) a RT durante 5 minutos antes del agregado de perclorato de 3-metil-2-metitio[1,3,4]tiadiazolio (**3a**) (0,7 mmol, 0,25 g). El residuo se sometió a cromatografía sobre gel de sílice (columna de

Alltec, 2 g de sílice) eluyendo con diclorometano que contenía del 0% al 1% de metanol.

Rendimiento= 0,050g, 22%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,25 (m, 4H), 1,50-1,66 (m, 3H), 1,71-1,79 (b, 1H), 2,28-2,33 (m, 1H), 3,21-3,27 (m, 1H), 3,40 (s, 3H), 4,38 (s, 1H), 7,42 (dd, 2H), 7,54 (dd, 2H).

MS (m/z) / M+1= 324/326

HPLC (pureza uv, λ= 214 nm)= 99,9%

Los siguientes compuestos se prepararon mediante el procedimiento descripto en el ejemlo I8 usando los intermedios y reactivos apropiados.

I8.1	5-(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-2-metoxi-fenol
I8.2	ácido 3-(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-benzoico
I8.3	ácido 3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-4-hidroxi-benzoico
I8.4	(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-(3-metanosulfonil-fenil)-amina

Ejemplo I9: R_1= (1R*, 2R*)-ciclohexil-2-ol, R_2= metilo, R_3= 4-(metanosulfonol)-fenilo

(1R*, 2R*)-2-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol

The compuesto I9 se preparó mediante el procedimiento descripto en el ejemplo I4 (protocolo A).

Perclorato de 3-metil-2-metiltio[1,3,4]tiadiazolio (3b) (0,372 mmol, 0,15 g), clorhidrato de trans-2-aminociclohexanol (0,410 mmol, 0,062 g) y trietilamina (0,7814 mmol, 0,109 ml) reaccionaron en etanol (1,5 ml). El producto crudo se cromatografió sobre gel de sílice dos veces con una mezcla de DCM:MeOH (98:2) para dar el producto del título.

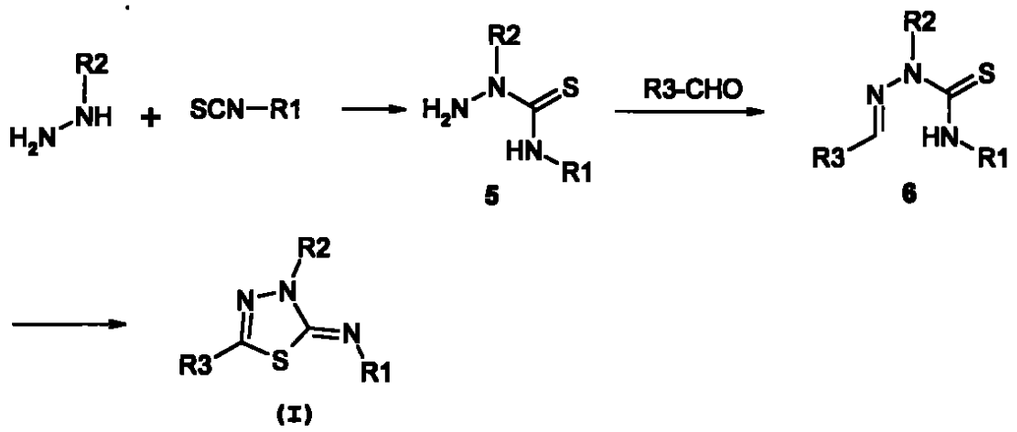
Rendimiento= 0,030 g, 23%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,37 (m, 5H), 1,60-1,78 (b, 3H), 1,81-1,90 (b, 1H), 3,3 (s, 3H), 3,32-3,40 (b, 1H), 3,52 (s, 3H), 4,53 (s, 1H), 7,89 (d, 2H), 8,01 (d, 2H).

MS (m/z) / M+1= 368/370

HPLC (pureza uv, λ= 214 nm)= 99,17%

Protocolo B



Intermedio 5: Protocolo B

Intermedio 5a: R_1= ciclohexilo, R_2= metilo

N-(ciclohexil)-1-metil hidrazincarbotioamida

El ciclohexilisotiocianato requerido (70,8 mmol, 10 g) se disolvió en metanol (35 ml) y esta solución se agregó gota a gota (30 min) a una solución de metilhidrazina (134,5 mmol, 7 ml) en agua (35 ml) a 0°C. Después de mezclar, la solución se dejó agitar a RT toda la noche. El precipitado se removió por filtración. El sólido se lavó con EtOH frío para dar 11,7 g del derivado esperado 5a.

Rendimiento= 88,7%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,25 (m,5H), 1,50-1,60 (m,1H), 1,60-1,70 (m,2H), 1,80-1,90 (m,2H), 3,40 (s,3H), 3,90-4,00 (m,1H), 4,80 (s,2H), 7,85 (d,1H).

MS (m/z) / M+1 = 188,33

Intermedio 5b: R_1= ciclohexilo, R_2= H

N-ciclohexil hidrazincarbotioamida

El ciclohexilisotiocianato requerido (141 mmol, 20 ml) se disolvió en metanol (30 ml) y esta solución se agregó gota a gota (35 min) a una solución agitada de hidrazinhidrato (423 mmol, 13,2 ml) en metanol (200 ml) a 0°C. Después de mezclar, la solución se dejó agitar a RT toda la noche. El precipitado se removió por filtración. El sólido se lavó con EtOH frío para dar 14,9 g del derivado esperado (5b).

Rendimiento= 61%

^{1}H-NMR (400MHz, DMSO) δ ppm : 1,10-1,35 (m,5H), 1,50-1,60 (m,1H), 1,60-1,75 (m,2H), 1,75-1,90 (m,2H), 4,00-4,10 (m,1H), 4,40 (s,2H), 7,50 (d,1H), 8,50 (s,1H).

MS (m/z) / M+1 =174,25

Intermedio 5c: R_1= metil éster del ácido 3-benzoico, R_2= H

Hidrazincarbotioamida de N-(metil éster del ácido 3-benzoico)

3-Metoxicarbonilisotiocianato (77,6 mmol, 15 g) se agregó gota a gota (30 min) a una solución agitada de hidrato de hidrazina (97 mmol, 4,7 ml) en metanol (40 ml) a -10°C. Después de agitar a -10°C durante 5 h, la solución se dejó agitar a temperatura ambiente toda la noche. El precipitado se filtró y se lavó con metanol frío para dar 15,4 g del compuesto esperado (rendimiento: 88%).

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,85 (s, 3H), 4,85 (brs, 1H), 7,43 (t, 1H), 7,68 (d, 1H), 7,87 (d, 1H), 8,33 (s, 1H), 9,23 (s, 1H).

MS (m/z) / M+1 = 226

Intermedio 6: PROTOCOLO B

Intermedio 6a: R_1= ciclohexilo, R_2= metilo, R_3= 2,4-diclorofenilo

N-ciclohexil-2-[(2,4-clorofenil)-metilen] hidrazincarbotioamida

Una suspensión de 2-metiltiosemicarbazida (5a) (2,67 mmol, 500 mg) en etanol (5 ml) y 2,4-diclorobenzaldehído (2,94 mmol, 515 mg) se calentó a 75°C durante 18 horas. Después de enfriar, el precipitado formado se filtró y se lavó con etanol frío para dar 876 mg del compuesto del título.

Rendimiento: 95,5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,25 (m, 1H), 1,25-1,35 (m, 2H), 1,35-1,55 (m, 2H), 1,60-1,70 (m, 1H), 1,70-1,80 (m, 1H), 1,90-2,00 (m, 2H), 3,80 (s, 3H), 4,10-4,30 (m, 1H), 7,50 (d, 1H), 7,70 (s, 1H), 8,00 (s, 1H), 8,20 (d, 1H), 8,50 (d, 1H).

EJEMPLO I: PROTOCOLO B

Ejemplo I10: R_1= ciclohexilo, R_2= metilo, R_2= 2,4-diclorofenilo
Ciclohexil-[5-(2,4-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidan]-amina

La tiosemicarbazona apropiada (preparada mediante el procedimiento decripto en el ejemplo 6a) (2,3 mmol, 800 mg) se suspendió en etanol (5 ml) y se agregó el oxidante $FeCl_3$, $6H_2O$ (5,06 mmol, 1,38 g) disuelto en etanol (5 ml). La mezcla se calentó a 75°C durante 19 h (control de TLC). El oxidante (1,15 mmol, 0,31 g) se agregó para permitir que se completara la reacción. La mezcla se concentró mediante la destilación del solvente y el material crudo se solubilizó en acetato de etilo. Las sales inorgánicas se removieron mediante la extracción con agua. La capa orgánica se lavó con una solución de NaCl, se secó bajo sulfato de magnesio, se filtró y se destiló para dar un residuo que se cromatografió sobre una columna de gel de sílice (usando un gradiente de solvente de acetato de etilo-ciclohexano comenzando con una razón de 5/95)

para aislar 230 mg de la tiadiazolina pura. El subproducto principalmente formado durante esta reacción es la 1,2,4-triazolin-5-tiona.

Rendimiento: 35%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,40 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,80 (m, 4H), 2,55-2,70 (m, 1H), 3,50 (s, 3H), 7,50 (d, 1H), 7,70-7,80 (m, 2H)

MS (m/z) / M+1= 344,1

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I10.1: R_1= ciclohexilo, R_2= metilo, R_3= 2-cloro-fenilo [5-(2-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

El compuesto I10.1 se preparó mediante el procedimiento descripto en I10 usando los intermedios y reactivos apropiados.

El residuo se sometió a cromatografía sobre gel de sílice, eluyendo con ciclohexano que contenía del 0% al 6% de AcOEt.

Rendimiento: 6%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,35 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,70 (m, 4H), 2,55-2,65 (m, 1H), 3,50 (s, 3H), 7,40-7,50 (m, 2H), 7,60 (d, 1H), 7,70 (d, 1H)

MS (m/z) / M+1= 310,2

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I11: R_1= ciclohexilo, R_2= metilo, R_3= (trifluorometil)-fenilo

Ciclohexil-[3-metil-5-(4-trifluorometil-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina

La tiosemicarbazona apropiada (preparada mediante el procedimiento descripto en el ejemplo 6a) (2 mmol, 700 mg) se suspendió en etanol (5 ml) y se agregó el oxidante $FeCl_3$, $6H_2O$ (4,4 mmol, 1,21 g) disuelto en etanol (5 ml). La mezcla se calentó a 75°C durante 19 h. La mezcla se concentró mediante la destilación del solvente y el material crudo se solubilizó en acetato de etilo. Las sales inorgánicas se removieron mediante la extracción con agua. La capa orgánica se lavó con una solución de NaCl, se secó bajo sulfato de magnesio, se filtró y se destiló para dar un residuo que se cromatografió sobre una columna de gel de sílice (usando un gradiente de solvente de acetato de etilo-ciclohexano como eluyente con un soporte 5/95) para aislar 290 mg de la tiadiazolina pura.
Rendimiento: 42%

005/14

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,25-1,50 (m, 5H), 1,60-1,70 (m, 1H), 1,75-1,90 (m, 4H), 2,65-2,75 (m, 1H), 3,60 (s, 3H), 7,85-7,95 (m, 4H)

MS (m/z) / M+1= 342,6

HPLC (pureza uv, λ= 214 nm). 99,9%

Ejemplo I12 R_1= ciclohexilo, R_2= metilo, R_3= 4-piridilo

Ciclohexil-(3-metil-5-piridin-4-il-3H-[1,3,4]tiadiazol-2-iliden)-amina

El compuesto I12 se preparó mediante el procedimiento descripto en el ejemplo I11 usando los intermedios y reactivos apropiados (protocolo B)

La mezcla se concentró mediante la destilacion bajo presión reducida y el residuo se disolvio en agua La mezcla acuosa luego se basificó con una solución saturada de $NaHCO_3$ y se extrajo con acetato de etilo La capa orgánica se lavó con una solución saturada de NaCl y se seco sopre sulfato de magnesio, se filtro y se destió para dar un residuo que se purifico mediante cromatografia sobre gel de silice (eluyente ciclohexano/acetato de etilo,95/5)

Rendimiento 80%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,55-2,70 (m, 1H), 3,55 (s, 3H), 7,60 (d, 2H), 8,65 (d, 2H)

MS (m/z) / M+1= 275,2

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I13: R_1= ciclohexilo, R_2= metilo, R_3= 3-cloro-fenilo [5-(3-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

Los compuestos I13 se prepararon mediante el procedimiento descripto en el ejemplo I10 usando los intermedios y reactivos apropiados (protocolo B).

El residuo se sometió a cromatografía sobre gel de sílice, eluyendo con ciclohexano que contenía del 0% al 6% de AcOEt.

Rendimiento: 23%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,55-2,70 (m, 1H), 3,50 (s, 3H), 7,45-7,55 (m, 2H), 7,55-7,65 (m, 1H), 7,70 (s, 1H)

MS (m/z) / M+1= 308

HPLC (pureza uv, λ= 214 nm): 99,9%

00676

Ejemplo I14: R_1= ciclohexilo, R_2= metilo, R_3= 4-ciano-fenilo

4-(5-Ciclohxilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo

Los compuestos I14 se prepararon mediante el procedimiento decripto en el ejemplo I10 usando los intermedios y reactivos apropiados (protocolo B).

El residuo se sometió a cromatografía sobre gel de sílice, eluyendo con ciclohexano que contenía del 0% al 8% de AcOEt.

Rendimiento: 10%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,80 (m, 4H), 2,60-2,70 (m, 1H), 3,55 (s, 3H), 7,80 (d, 2H), 7,90 (d, 2H)

MS (m/z) / M+1= 299,2

HPLC (pureza uv, λ= 214 nm): 99,3%

Ejemplo I15: R_1= ciclohexilo, R_2= metilo, R_3= 4-metilsulfonil-fenilo

Ciclohexil-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

Los compuestos I15 se prepararon mediante el procedimiento descripto en el ejemplo I10 usando los intermedios y reactivos apropiados (protocolo B).

El residuo se sometió a cromatografía sobre gel de sílice, eluyendo con ciclohexano que contenía del 0% al 10% de AcOEt. El protocolo D dio mejor rendimiento para preparar I15.

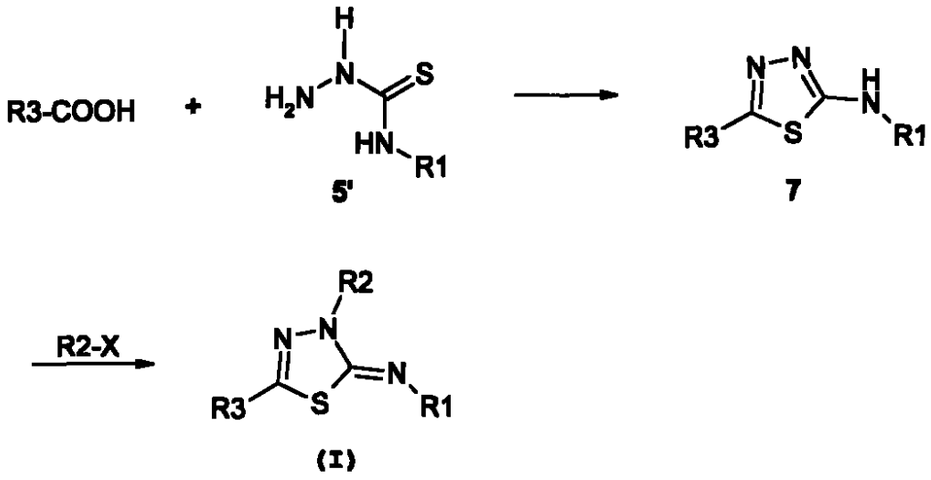
Rendimiento: 3%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,35 (m, 5H), 1,45-1,55 (m, 1H), 1,60-1,75 (m, 4H), 2,50-2,60 (m, 1H), 3,20 (s, 3H), 3,45 (s, 3H), 7,80 (d, 2H), 7,90 (d, 2H).

MS (m/z) / M+1= 352,5

HPLC (pureza uv, λ= 214 nm): 87,3%

Protocolo C



00578

Intermedio 7: PROTOCOLO C

Intermedio 7a: R_1= ciclohexilo, R_3= 4-cloro-3-sulfamoil-fenilo

2-Cloro-5-(5-ciclohexilamino-[1,3,4]tiadiazol-2-il)-bencensulfonamida

A una mezcla de ácido 4-cloro-3-sulfamoil-benzoico (6,36 mmol, 1,5 g), tiosemicarbazida (5b) (6,36 mmol, 1,10 g) en dioxano (40 ml) a 60°C, se agregó $POCl_3$ (6,36 mmol, 600 µl) y la mezcla se calentó a reflujo durante 2h30 y 16 h a RT. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo que se basificó con una solución diluida de NH_4OH. El precipitado amarillo obtenido se recogió mediante filtración, se lavó con agua antes de secar bajo vacío sobre P_2O_5 para dar 2 g del producto deseado.

Rendimiento= 84%;

^1H (400MHz, DMSO) δ ppm: 1,10-1,37 (m, 5H), 1,55 (m, 1H), 1,70 (m, 2H), 1,98 (m, 2H), 3,55 (m, 1H), 7,66-7,82 (m, 3H), 7,90 (m, 1H); 8,25-8,37 (br, 2H).

MS (m/z) / M+1 = 373/375

Intermedio 7b: R_1= ciclohexilo, R_3= 2,4-dicloro-5-sulfamoil-fenilo

2,4-Dicloro-5-(5-ciclohexilamino-[1,3,4]tiadiazol-2-il)-bencensulfonamida

A una mezcla de ácido 2,4-diclorobenzoico (1,85 mmol, 500 mg), tiosemicarbazida (5b) (1,85 mmol, 320 mg) en dioxano anhidro (10 ml) a 70°C-80°C, se agregó $POCl_3$ (1,85 mmol, 173 µl) y la mezcla se calentó a 95°C durante 5 horas. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo que se basificó a pH 8-7 con una solución saturada de $NaHCO_3$. El precipitado obtenido se recogió mediante filtración, se lavó con agua y se purificó mediante cromatografía sobre gel de sílice usando ciclohexano/acetato de etilo como eluyente para dar 351 mg del compuesto del título.

Rendimiento: 46,3%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,40 (m, 5H), 1,50-1,65 (m, 1H), 1,65-1,80 (m, 2H), 1,90-2,05 (m, 2H), 3,50-3,70 (m, 1H), 7,85 (d, 2H), 8,05 (s, 1H), 8,20-8,40 (m, 1H), 8,60 (s, 1H).

MS (m/z) / M+1= 407,1

HPLC (pureza uv, λ= 214 nm): 97,1%

Intermedio 7c: R_1= ciclohexilo, R_3= 3-tienilo

Ciclohexil-(5-tiofen-3-il-[1,3,4]tiadiazol-2-il)-amina

A una mezcla de ácido 3-tiofencarboxílico (3,9 mmol, 500 mg), tiosemicarbazida **5b** (3,9 mmol, 675 mg) en dioxano anhidro (10 ml) a 60°C-65°C, se agregó $POCl_3$ (5 mmol, 473 µl) y la mezcla se calentó a 95°C durante 5 horas. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo que se basificó a pH 8-7 con una solución saturada de $NaHCO_3$. El precipitado obtenido se recogió bajo vacío para proporcionar 965 mg del compuesto deseado **(7a)**.
Rendimiento: 93%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,40 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,75(m, 2H), 1,90-2,00 (m, 2H), 3,45-3,55 (m, 1H), 7,45 (d, 1H), 7,65 (d, 1H), 7,80 (d, 1H), 7,85 (s, 1H).

Intermedio 7d: R_1= ciclohexilo, R_3= 3-cloro-2,6-dimetoxifenilo
[5-(3-Cloro-2,6-dimetoxi-fenil)-[1,3,4]tiadiazol-2-il]-ciclohexil-amina

A una mezcla de ácido 3-cloro-2,6-dimetoxibenzoico (2,3 mmol, 500 mg), tiosemicarbazida **5b** (2,3 mmol, 399 mg) en dioxano anhidro (10 ml) a 70°C-80°C, se agregó $POCl_3$ (2,3 mmol, 215 µl) y la mezcla se calentó a 95°C durante 5 horas. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo que se basificó a pH 8-7 con una solución saturada de $NaHCO_3$. El precipitado obtenido se recogió mediante

filtración, se lavó con agua y se secó bajo vacío. El sólido se sometió a cromatografía rápida eluyendo con acetato de etilo/ciclohexano para dar 115 mg del compuesto del título.

Rendimiento: 14%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,80 (m, 2H), 1,95-2,05 (m, 2H), 3,50-3,60 (m, 1H), 3,70 (s, 3H), 3,80 (s, 3H), 7,00 (d, 1H), 7,55 (d, 1H), 7,75 (d, 1H).

MS (m/z) / M+1 = 354,1

Intermedio 7e: R_1= ciclohexilo, R_3= 3-bromo-4-metoxifenilo

[5-(3-Bromo-4-metoxi-fenil)-[1,3,4]tiadiazol-2-il]-ciclohexil-amina

A una mezcla de ácido 3-bromo-4-metoxibenzoico (2,16 mmol, 500 mg), tiosemicarbazida **5b** (2,16 mmol, 375 mg) en dioxano anhidro (10 ml) a 60°C-65°C, se agregó $POCl_3$ (2,8 mmol, 262 µl) y la mezcla se calentó a 95°C durante 5 horas. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo que se basificó a pH 8-7 con una solución saturada de $NaHCO_3$. El precipitado obtenido se recogió mediante filtración, se lavó con agua y se secó bajo vacío. El sólido se solubilizó en 50 ml de diclorometano/metanol (7/3) al cual se agregó resina de morfolina (13,88 mmol, 4 g). La mezcla se

agitó toda la noche para remover el exceso de ácido. La sal de morfolina de resina se filtró y la capa orgánica se concentró mediante la destilación bajo presión reducida para dar 740 mg del producto purificado (7e).

Rendimiento: 92,8%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,40 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,75 (m, 2H), 1,90-2,00 (m, 2H), 3,45-3,55(m, 1H), 7,45 (dd, 1H), 7,65 (dd, 1H), 7,80 (dd, 1H), 7,85 (dd, 1H).

Intermedio 7f: R_1= ciclohexilo, R_3= 2-pirazinilo

Ciclohexil-(5-pirazin-2-il-[1,3,4]tiadiazol-2-il)-amina

A una mezcla de ácido 2-pirazino carboxílico (2,885 mmol, 0,358 g), tiosemicarbazida (5b) (2,885 mmol, 0,5 g) en dioxano anhidro (10 ml), se agregó oxicloruro de fósforo (3,751 mmol, 0,350 ml) a 90°C y la mezcla se calentó a 95°C durante 5 horas. La mezcla se basificó a pH 7 con una solución saturada de bicarbonato de sodio, luego se extrajo con EtOAc. La fase orgánica se secó sobre $MgSO_4$ y se evaporó hasta secarse para dar el producto esperado.

Rendimiento= 0,6 g, 79,6%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,44 (m, 5H), 1,56-1,63 (b, 1H), 1,70-1,77 (b, 2H), 2,00-2,05 (b, 2H), 3,60-3,68 (b, 1H), 8,22 (d, 1H), 8,67-8,69 (m, 2H), 9,28 (s, 1H).

Intermedio 7g: R_1= ciclohexilo, R_3= 3,4-dihidroxifenilo

4-(5-Ciclohexilamino-[1,3,4]tiadiazol-2-il)-bencen-1,2-diol

A una mezcla de ácido 3,4-dihidroxibenzoico (2,885 mmol, 0,445 g), tiosemicarbazida (5b) (2,885 mmol, 0,500 g) en dioxano anhidro (10 ml), se agregó oxicloruro de fósforo (3,751 mmol, 0,350 ml) a 90°C y la mezcla se calentó a 95°C durante 5 horas. La mezcla se basificó con una solución saturada de bicarbonato de sodio a pH 7, luego se agitó a RT toda la noche. El precipitado se filtró, se lavó con hexano, luego se secó para dar el compuesto del título.

Rendimiento: 71%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,39 (m, 5H), 1,55-1,62 (b, 1H), 1,70-1,78 (b, 2H), 1,95-2,00 (b, 2H), 3,48-3,53 (b, 1H), 6,80 (d, 1H), 6,98 (d, 1H), 7,19 (s, 1H), 7,68 (d, 1H), 9,20-9,40 (b, 2H).

Intermedio 7h: R_1= ciclohexilo, R_3= 4-cloro-fenilo

[5-(4-Cloro-fenil)-[1,3,4]tiadiazol-2-il]-ciclohexil-amina

Se suspendió tiosemicarbazona (6b) (obtenida de 5b siguiendo el protocolo 6b) (10 mmol, 3 g) se suspendió en etanol (50 ml) y se agregó el oxidante $FeCl_3$, $6H_2O$ (23 mmol, 6,3 g). La mezcla se calentó a reflujo durante 3 h. La mezcla se concentró mediante la destilación del solvente y el material crudo se

solubilizó en acetato de etilo. La capa orgánica se lavó con agua, se secó bajo sulfato de magnesio, se filtró y se destiló para dar un residuo sometido a otro proceso oxidativo con $FeCl_3$, $6H_2O$ (3g) en etanol (50 ml). La mezcla se calentó a reflujo durante 3 h y 12 h a RT. La mezcla se concentró mediante la destilación del solvente y el material crudo se solubilizó en acetato de etilo. Las sales inorgánicas se removieron mediante la extracción con agua. La capa orgánica se lavó con una solución de NaCl, se secó bajo sulfato de magnesio, se filtró y se destiló para dar un residuo que se trituró y se lavó con ciclohexnao para dar 2,5 g del producto del título.

Rendimiento: 85%

^{1}H-NMR (400MHz, DMSO) δ ppm: 0,95-1,22 (m, 5H), 1,35-1,45 (b, 1H), 1,50-1,60 (m, 2H), 1,80-1,87 (m, 2H), 3,32-3,42 (b, 1H), 7,35 (d, 2H), 7,55 (d, 2H), 7,75 (d, 1H)

MS (m/z) / M+1 = 294,1

HPLC (pureza uv, λ= 214 nm): 97,21%

Intermedio 71: R_1= ciclohexilo, R_3= 3-cloro-4-hidroxi-5-metoxifenilo

2-Cloro-4-(5-ciclohexilamino-[1,3,4]tiadiazol-2-il)-6-metoxi-fenol

A una mezcla del ácido 3-cloro-4-hidroxi-5-metoxibenzoico (2,468 mmol, 500 g), tiosemicarbazida (5b) (2,468 mmol, 427 mg) en dioxano (10 ml) a 65°C, se agregó $POCl_3$ (3,2 mmol, 300 µl) y la mezcla se calentó a 95°C durante 3h30. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo que se basificó con una solución de NH_4OH. El precipitado obtenido se recogió mediante filtración, se lavó con agua antes de secar bajo vacío sobre P_2O_5 para dar 675 mg del producto deseado.

Rendimiento= 80%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,36 (m, 5H), 1,53-1,63 (m, 1H), 1,67-1,80 (m, 2H), 1,95-2,05(m, 2H), 3,45-3,57 (m, 1H), 3,90 (s, 3H), 7,25 (s, 1H); 7,30 (s, 1H), 7,85 (d, 1H), 9,90 (s, 1H)

Intermedio 7j: R_1= metil éster del ácido 3-benzoico, R_3= 3-ciano-fenilo

Metil éster del ácido 3-[5-(3-Ciano-fenil)-[1,3,4]tiadiazol-2-ilamino]-benzoico

A una mezcla de ácido 3-cianobenzoico (2,92 mmol, 0,43 g), (5c) (3 mmol, 0,7 g) en dioxano (10 ml) a 85°C, se agregó $POCl_3$ (3,8 mmol, 350 µL) y la mezcla se calentó a 95°C durante 3h30. El solvente se removió mediante destilación bajo presión

reducida para dar un material crudo que se basificó con una solución saturada acuosa de $NaHCO_3$. El precipitado obtenido se recogió mediante filtración, se lavó sucesivamente con agua y con éter antes de secarse bajo vacío para dar 0,5 g del producto deseado (rendimiento: 49%).

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,88 (s, 3H), 7,53 (t, 1H), 7,63 (d, 1H), 7,72 (t, 1H), 7,86 (d, 1H), 7,96 (d, 1H), 8,23 (d, 1H), 8,32 (s, 1H), 8,43 (s, 1H), 10,89 (s, 1H).

MS (m/z) / M+1 = 337

Intermedio 7k: R_1= metil éster del ácido 3-benzoico, R_3= 2-piridilo

Metil éster del ácido 3-(5-piridin-2-il-[1,3,4]tiadiazol-2-ilamino)-benzoico

A una mezcla de ácido picolínico (2,92 mmol, 0,36 g), (5c) (3 mmol, 0,7 g) en dioxano (10 ml) a 85°C, se agregó $POCl_3$ (3,8 mmol, 350 µL) y la mezcla se calentó a 95°C durante 5 h. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo. Se agregó metanol y el precipitado obtenido se recogió mediante filtración, se lavó con metanol y se secó bajo vacío para dar 0,59 g (61%) del producto deseado. El material crudo se unió en el paso siguiente sin purificación.

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,8 (s, 3H), 7,5 (m, 2H), 7,6 (d, 1H), 7,88 (d, 1H), 7,98 (t, 1H), 8,12 (d, 1H), 8,42 (s, 1H) , 8,63 (d, 1H), 10,9 (s, 1H).

MS (m/z) / M+1 = 313/314/315

EJEMPLO I: PROTOCOLO C

Ejemplo I16: R_1= ciclohexilo, R_2= metilo, R_3= 2,4-dicloro-5-sulfamoil-fenilo

2,4-Dicloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencensulfonamida

A una solución de 1,3,4-tiadiazol **7b** (0,195 mmol, 80 mg) en dioxano anhidro (10 ml), se agregó sulfonato de metiltrifluorometano (0,23 mmol, 27 µL). La mezcla resultante se agitó durante 24 h. A esta solución se agregó 0,527 mmol (64 µL) de sulfonato de metiltrifluorometano para permitir que se complete la reacción, y 0,585 mmol (82 µL) de trietilamina. El filtrado se concentró mediante la destilación bajo presión reducida. El producto se purificó mediante cromatografía de columna sobre gel de sílice (eluido con ciclohexano/acetato de etilo, 80/20) para dar 48 mg del producto del título.

Rendimiento: 58%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,60-2,70 (m, 1H), 3,55 (s, 3H), 7,80 (d, 2H), 8,0 (s, 1H), 8,35 (s, 1H).

MS (m/z) / M+1: 421,3

HPLC (pureza uv, λ= 214 nm): 99,4%

Ejemplo I17: R_1= ciclohexilo, R_2= metilo, R_3= 3-tienilo

Ciclohexil-(3-metil-5-tiofen-3-il-3H-[1,3,4] tiadiazol-2-iliden)-amina

A una solución de 1,3,4-tiadiazol 7c (0,75 mmol, 200 mg) en dioxano anhidro (10 ml), se agregó sulfonato de metiltrifluorometano (1,13 mmol, 128 µL). La mezcla resultante se agitó durante 24 h. A esta solución se agregó 0,225 mmol (26 µL) de metiltrifluorometanosulfonato para permitir que la reacción se complete, y 0,675 mmol (94 µL) de trietilamina. La mezcla se concentró mediante destilación bajo presión reducida y el residuo se disolvió en agua. La mezcla acuosa luego se basificó (pH= 5-6) con una solución saturada de $NaHCO_3$ con acetato de etilo. La capa orgánica se saturó con NaCl y se secó sobre sulfato de magnesio, se filtró y se destiló para dar un residuo que se purificó mediante cromatografía sobre gel de sílice, eluyendo con ciclohexano que contenía del 0% al 15% de AcOEt para proporcionar 80 mg del producto deseado.

Rendimiento: 38%

^{1}H-NMR (400MHz, DMSO): δ ppm= 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,7-1,8 (m, 4H), 2,55-2,65 (m, 1H), 3,45 (s, 3H), 7,40 (d, 1H), 7,70 (d, 1H), 7,85 (s, 1H).

MS (m/z) / M+1= 280,23

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I17.1: R_1= ciclohexilo, R_2= metilo, R_3= 3,5-dicloro-feilo

Ciclohexil-[5-(3,5-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

El compuesto I17.1 se preparó mediante el procedimiento descripto en el ejemplo I17 usando los intermedios y reactivos apropiados.

Rendimiento 43%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,35 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,90 (m, 4H), 2,55-2,65 (m, 1H), 3,50 (s, 3H), 7,65 (s, 2H), 7,70 (s, 1H)

MS (m/z) / M+1= 342,2

HPLC (pureza uv, λ = 214 nm): 99,9%

El compuesto I17.2 se preparó mediante el procedimiento descripto en el ejemplo I17 usando los intermedios y reactivos apropiados.

I17.2	Ciclohexil-[5-(2-etil-5-metil-2H-pirazol-3-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

Ejemplo I18: R_1= ciclohexilo, R_2= metilo, R_3= 3-cloro-2,6-dimetoxifenilo

[5-(3-Cloro-2,6-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

A una solución del 1,3,4-tiadiazol **7d** (0,226 mmol, 80 mg) en dioxano anhidro (10 ml), se agregó metiltrifluoro metanosulfonato (0,27 mmol, 31 µL). La mezcla resultante se agitó durante 24 h. A esta solución se agregó 0,068 mmol (7 µL) de metiltrifluorometanosulfonato para permitir que se complete la reacción. La mezcla se concentró mediante destilación bajo presión reducida y el residuo se disolvió en agua. La mezcla acuosa luego se basificó (pH= 5-6) con una solución saturada de $NaHCO_3$ y se extrajo con acetato de etilo. La capa orgánica se lavó con una solución saturada de NaCl y se secó sobre sulfato de magnesio, se filtró y se destiló para dar un residuo que se purificó mediante cromatografía sobre gel de

sílice (eluyente: ciclohexano/acetato de etilo, 80/20). Se obtuvieron 11 mg del producto deseado.

Rendimiento: 13%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,80 (m, 4H), 2,50-2,60 (m, 1H), 3,50 (s, 3H), 3,75 (s, 3H), 3,80 (s, 3H), 7,00 (d, 1H), 7,60 (d, 1H)

MS (m/z) / M+1= 368,26

HPLC (pureza uv, λ= 214 nm): 99,7%

El compuesto I18.1 se preparó mediante el procedimiento descripto en el ejemplo I18 usando los intermedios y reactivos apropiados:

I18.1	Ciclohexil-(5-isoxazol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-amina

Ejemplo I18.2: R_1= ciclohexilo, R_2= metilo, R_3= 2-(5-piridin-2-il)-tienilo

Ciclohexil-[3-metil-5-(5-piridin-2-il-tiofen-2-il)-3H-[1,3,4]tiadiazol-2-iliden]-amina

El compuesto I18.2 se preparó mediante el procedimiento descripto en el ejemplo I18 usando los intermedios y reactivos apropiados. El residuo se purificó mediante cromatografía

sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 10% de acetato de etilo.

Rendimiento: 57%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,35 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,80 (m, 4H), 2,55-2,65 (m, 1H), 3,45 (s, 3H), 7,30 (m, 1H), 7,35 (d, 1H), 7,80 (d, 1H), 7,85 (m, 1H), 7,95 (d, 1H), 8,55 (d, 1H).

MS (m/z) / M+1= 357,3

HPLC (pureza uv, λ= 214 nm): 99,5%

Ejemplo I18.3: R_1= ciclohexilo, R_2= metilo, R_3= 3,5-dihidroxi-4-metoxi-fenilo

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ático trifluorometanosulfónico

El compuesto I18.3 se preparó desde el 1,3,4-tiadiazol 7 apropiado preparado mediante el procedimiento descripto en el ejemplo I18. En este caso particular, la mezcla se concentró y el precipitado formado se filtró y se lavó con acetato de etilo para dar el compuesto esperado como una sal del ácido trifluorometanosulfónico.

Rendimiento: 45%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1-1,40 (m, 5H), 1,45-1,65 (m, 1H), 1,65-1,75 (m, 2H), 1,85-1,95 (m, 2H), 3,05-3,20 (m, 1H), 3,6 (s, 3H), 4,00 (bs, 3H), 6,65 (s, 2H), 9,60 (bs, 2H), 10,00 (bs, 1H).

MS (m/z) / M+1= 336,4

HPLC (pureza uv, λ= 214 nm): 99,7%

Ejemplo I18.4: R_1= ciclohexilo, R_2= metilo, R_3= 3-hidroxi-4,5-dimetoxi-fenilo

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluorometanosulfónico

El compuesto I18.4 se preparó desde el 1,3,4-tiadiazol 7 apropiado preparado mediante el procedimiento descripto en el ejemplo I18. En este caso particular, la mezcla se concentró y el precipitado formado se filtró y se lavó con acetato de etilo para dar el compuesto esperado como una sal del ácido trifluorometanosulfónico.

Rendimiento: 11%

1H-NMR (400MHz, DMSO) δ ppm: 1,10-1,50 (m, 5H), 1,60-1,70 (m, 1H), 1,75-1,85 (m, 2H), 1,95-2,10 (m, 2H), 3,10-3,25 (m, 1H), 3,75 (s, 3H), 3,85 (s, 6H), 6,85 (s, 1H), 6,95 (s, 1H), 9,80 (bs, 1H), 9,90 (bs, 1H).

MS (m/z) / M+1= 350,45

HPLC (pureza uv, λ= 214 nm) 99,9%

Ejemplo I18 5 R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-fenilo

[5-(4-Cloro-fenil)-3-metil-3-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

El compuesto I18 5 se preparo mediante el procedimiento descripto en el ejemplo I18 usando los intermedios y reactivos apropiados

^{1}H-NMR (400MHz, DMSO) δ ppm 1,20-1,40 (m, 5H), 1,57-1,63 (m, 1H), 1,70-1,82 (m, 4H), 2,60 (br, 1H), 3,50 (s, 3H), 7,52(d, 2H), 7,65 (d, 2H)

MS (m/z) / M+1= 308/310

HPLC (pureza uv, λ= 214nm) 94,24%

Ejemplo I18 6 R_1= ciclohexilo, R_2= metilo, R_3= 3-cloro-4-hidroxi-5-metoxi-fenilo

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-6-metoxi-fenol, compuesto con ácido 1,1,1-trifluoro-metanosulfónico

El compuesto I18 6 se preparo desde el 1,3,4-tiadiazol 7i apropiado A una solución del intermedio 7i (2 mmol, 675 mg)

en dioxano anhidro (10 ml), se agregó sulfonato de metiltrifluorometano (3 mmol, 337 µl). La mezcla resultante se agitó durante 48 h para dar un precipitado. La mezcla se filtró y se lavó con acetato de etilo para dar 400 mg del producto de seado como una sal del ácido trifluorometanosulfónico.

Rendimiento: 40%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,55 (m, 5H), 1,60-1,70 (m, 1H), 1,76-1,88 (m, 2H), 2,00-2,11 (m, 2H), 3,11-3,25 (m, 1H), 3,85 (s, 3H), 3,95 (s, 3H), 7,30 (s, 1H), 7,48 (s, 1H), 9,90 (s, 1H), 10,50 (s, 1H).

MS (m/z) / M+1= 354/356

HPLC (pureza uv, λ= 214 nm): 99,4%

Ejemplo I19: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-sulfamoil-fenilo

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencensulfonamida

A una solución de 1,3,4-tiadiazol 7a (0,215 mmol, 80 mg) en dioxano anhidro (10 ml), se agregó sulfonato de metiltrifluorometano (0,247 mmol, 29 µl). La mezcla resultante se agitó durante 24 h. A esta solución se agregó (0,065 mmo, 7 µl) sulfonato de metiltrifluorometano para permitir que la

reacción se completara. El filtrado se concentró mediante la destilación bajo presión reducida y el residuo se disolvió en agua. La mezcla acuosa luego se basificó (pH= 5-6) con una solución saturada de $NaHCO_3$ y se extrajo con acetato de etilo. La capa orgánica se lavó con una solución saturada de NaCl y se secó sobre sulfato de magnesio, se filtró y se destiló para dar un residuo que se purificó por cromatografía sobre gel de sílice (eluido con un gradiente de ciclohexano/acetato de etilo) para dar 59 mg del producto puro.

Rendimiento: 71%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,25-1,55 (m, 5H), 1,65-1,75 (m, 1H), 1,75-1,95 (m, 4H), 2,70-2,80 (m, 1H), 3,65 (s, 3H), 7,80-7,95 (m, 4H), 8,30 (dd, 1H).

MS (m/z) / M+1: 387,3

HPLC (pureza uv, λ= 214 nm): 99,7%

Ejemplo I19.1: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-N,N-dietil-3-sulfonamida-fenilo

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencensulfonamida

A una mezcla del compuesto I19 (0,258 mmol, 0,100 g), sulfato de hidrógeno de tetra-n-butilamonio (0,0258 mmol, 0,090 g), hidróxido de sodio acuoso al 50% (0,300 ml) y tolueno (2,2

ml), se agregó bromuro de etilo (0,310 mmol, 0,23 ml). La reacción se agitó a RT durante 2 h y luego se calentó a 90°C durante 1h30 antes de un segundo agregado de bromuro de etilo (0,310 mmol, 0,023 ml). La mezcla se calentó a 90°C durante 2h30 y los volátiles se removieron por destilación. El material crudo se solubilizó con acetato de etilo y la capa orgánica se lavó con solución salina, se secó sobre $MgSO_4$ y se concentró bajo presión reducida para dar 0,1 g del producto esperado como un sólido blanco.

Rendimiento= 87,7%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,00 (t, 6H), 1,10-1,32 (b, 5H), 1,48-1,54 (m, 1H), 1,65-1,73 (b, 4H), 2,53-2,62 (b, 1H), 3,20-3,30 (m, 4H), 3,48 (s, 3H), 7,68-7,79 (m, 2H), 8,11 (s, 1H).

MS (m/z) / M+1= 443/445

HPLC (pureza uv, λ= 214 nm)= 99,72%

Ejemplo I19.2: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-(4-metil-piperazin-1-sulfonil)-fenilo

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina

A una solución de I19 (0,516 mmol, 0,2 g) en DMF (13 ml) se agregaron carbonato de potasio (1,548 mmol, 0,214 g) y agua (3 ml). La mezcla se agitó a RT hasta que que se obtiene una

solución homogénea y luego se agregó el clorhidrato de bis-(2-cloro-etil)metil-amina (0,516 mmol, 0,10 g). Después de un día de agitación, la mezcla se calentó a 80°C durante 15 h. Los solventes luego se evaporaron y el material crudo se solubilizó en diclormetano. La capa orgánica se lavó con una solución saturada de bicarbonato de sodio, luego con solución salina. Después de la filtración, el filtrado se secó sobre $MgSO_4$ y se concentró mediante destilación. El material crudo se cromatografió sobre gel de sílice, eluyendo con diclorometano que contenía del 0% al 5% de metanol. El producto sólido se lavó luego con acetato de etilo.

Rendimiento= 10%

Yield= 10%

^{1}H-NMR (400MHz, $CDCl_3$ + D_2O) δ ppm: 1,20-1,48 (m, 5H), 1,62-1,68 (m, 1H), 1,79-1,89 (m, 4H), 2,45 (s, 3H), 2,45 (t, 4H), 2,55-2,65 (m, 1H), 3,33 (t, 4H), 3,60 (s, 3H), 7,52 (d, 1H), 7,72 (d, 1H), 8,24 (s, 1H).

MS (m/z) / M+1= 470

HPLC (pureza uv, λ= 214 nm): 99,53%

Ejemplo I19.3: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-[(piridin-4-ilmetil)-sulfamoil]-fenilo

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencensulfonamida

A una mezcla de I19 (0,258 mmol, 0,1 g), trietilamina (0,516 mmol, 0,072 ml) y ácido acético (0,516 mmol, 0,03 ml) en 1,2-dicloroetano, se agregó carboxaldehído de 4-piridina (0,387 mmol, 0,037 ml). La mezcla se enfrió a 0°C y se agregó triacetoxiborohidruro de sodio (0,516 mmol, 0,135 g). Después de 24 h de agitación a RT, se agregaron las mismas cantidades de borohidruro y aldehído y la reacción se agitó durante 15 h.

La mezcla luego se filtró y el filtrado se diluyó con diclorometano, se lavó con agua, solución salina, se secó sobre $MgSO_4$, se filtró y luego se evaporó hasta secarse. El residuo se purificó sobre gel de sílice eluyendo con diclorometano que contenía del 0% al 7% de metanol. El producto sólido luego se lavó con éter para dar el producto del título.

Rendimiento= 40%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,39 (m, 5H), 1,54-1,60 (m, 1H), 1,70-1,80 (m, 4H), 2,60-2,67 (m, 1H), 3,50 (s, 3H), 4,18 (s, 2H), 7,22 (d, 2H), 7,67 (dd, 1H), 7,76 (dd, 1H), 8,06 (d, 1H), 8,39 (d, 2H), 8,73-8,78 (b, 1H).

MS (m/z) / M+1= 478

HPLC (pureza uv, λ= 214 nm): 99,99%

Ejemplo I19.4: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-(2-morfolin-4-il-etil-sulfamoil)-fenilo

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencensulfonamida

2-Cloro-N-(2-cloro-etil)-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencensulfonamida se preparó mediante el procedimiento descripto en el ejemplo I19.3 usando un aldehído apropiado e I19. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contiene del 0% al 20% de acetato de etilo seguido por una elución isocrática con acetato de etilo/ciclohexano (4/6).
Rendimiento= 84%

A una mezcla de este intermedio (0,866 mmol, 0,390 g), en presencia de yoduro de sodio en etanol (10 ml), se agregó morfolina (8,66 mmol, 0,756 ml). Después de 15 h a reflujo, la mezcla se evaporó hasta secarse y el material crudo se basificó con una solución saturada de bicarbonato de sodio. Después de la extracción con acetato de etilo, la capa orgánica se lavó con solución salina, se secó sobre $MgSO_4$, se filtró y luego se evaporó hasta secarse. El residuo se purificó mediante cromatografía seobre gel de sílice eluyendo

con un gradiente de ciclohexano que contenía del 0% al 50% de acetato de etilo.

Rendimiento= 65%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,50 (m, 5H), 1,61-1,69 (m, 1H), 1,80-1,89 (b, 4H), 2,30-2,39 (m, 4H), 2,41-2,49 (m, 2H), 2,59-2,68 (m, 1H), 3,00-3,09 (m, 2H), 3,60-3,73 (m, 7H), 5,81-5,89 (b, 1H), 7,54 (d, 1H), 7,73 (d, 1H), 8,32 (s, 1H).

MS (m/z) / M+1= 500/501

HPLC (pureza uv, λ= 214 nm): 97,76%

Ejemplo I19.5: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-etilsulfamoil-fenil

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencensulfonamida

El compuesto del título se preparó como se describió en el ejemplo I19.3. En este caso particular, se usó y se agregó una vez un gran exceso de acetaldehído (20 equivalentes) y triacetoxi borohidruro (4 equivalentes).

Rendimiento= 50%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,13 (t, 3H), 1,22-1,50 (m, 5H), 1,61-1,68 (m, 1H), 1,78-1,87 (b, 4H), 2,57-2,64 (m, 1H), 2,97-3,04 (q, 2H), 3,60 (s, 3H), 4,90 (t, 1H), 7,53 (d, 1H), 7,77 (d, 1H), 8,30 (s, 1H).

MS (m/z) / M+1= 415/416

HPLC (pureza uv, λ= 214 nm): 99,36%

Ejemplo I19.6: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-[etil-(2-morfolin-4-il-etil)-sulfamoil]-fenilo
2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencensulfonamida

A una mezcla de I19.4 (0,100 mmol, 0,05 g), sulfato de hidrógeo de N-tetrabutil amonio (0,02 mmol, 0,008 g), se agregó una solución de 50% de hidróxido de sodio (1,25 mmol, 0,1 ml) en tolueno (2 ml), bromuro de etilo (1 mmol, 0,075 ml). La mezcla se calentó a 90°C durante 5 h y luego se evaporó hasta secarse. El residuo se solubilizó en acetato de etilo y la capa orgánica se se lavó con solución salina, se secó sobre $MgSO_4$, se filtró y luego se destiló bajo vacío. El material crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con una mezcla de acetato de etilo/ciclohexano a una razón de 1/9 luego 2/8 para dar el producto esperado.
Rendimiento= 60%
^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,13 (t, 3H), 1,22-1,45 (m, 5H), 1,61-1,68 (m, 1H), 1,78-1,84 (b, 4H), 2,38-2,43 (m, 4H), 2,50-

2,53 (t, 2H), 2,57-2,64 (m, 1H), 3,40-3,50 (m, 4H), 3,60-3,65 (m, 7H), 7,50 (d, 1H), 7,70 (d, 1H), 8,30 (s, 1H).

MS (m/z) / M+1 = 528/529

HPLC (pureza uv, λ= 214 nm): 98,57%

Ejemplo I19.7: R_1= ciclohexilo, R_2= metilo, R_3= 4-Cloro-3-[isopropil-(2-morfolin-4-il-etil)-sulfamoil]-fenilo 2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencensulfonamida

El compuesto del título se preparó como se describió en el ejemplo I19.6 con 13 equivalentes de bromuro de isopropilo. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 20% de acetato de etilo.

Rendimiento= 74%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,50 (d, 6H), 1,22-1,47 (m, 5H), 1,61-1,68 (m, 1H), 1,78-1,83 (b, 4H), 2,44-2,50 (m, 4H), 2,57-2,63 (m, 3H), 2,47-2,51 (t, 2H), 3,60 (s, 3H), 3,68-3,70 (m, 4H), 3,98-4,04 (m, 1H), 7,50 (d, 1H), 7,70 (d, 1H), 8,30 (s, 1H).

MS (m/z) / M+1= 542/543

HPLC (pureza uv, λ= 214 nm): 96,86%

Ejemplo I19.8: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-{etil-[2-(2-metoxi-etoxi)-etil]-sulfamoil}-fenilo

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencensulfonamida

A una solución de I19.5 (0,241 mmol, 0,1 g) en EtOH (4 ml), se agregó carbonato de potasio (0,289 mmol, 0,040 g) y luego la mezcla de la reacción se calentó a reflujo durante 30 minutos antes del agregado de 1-bromo-2-(2-metoxietoxi)etano (0,289 mmol, 0,040 ml). Después de 3 h a reflujo, se agregaron 2,4 equivalentes del derivado de bromo y la mezcla se mantuvo a reflujo durante otras 15 h. La mezcla luego se evaporó hasta secarse y el residuo se diluyó en agua y se extrajo con diclorometano. La capa orgánica se lavó con agua, solución salina, se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse. El material crudo se purificó mediante cromatografía sobre gel de sílice con un gradiente de ciclohexano que contenía del 10% al 60% de acetato de etilo.

Rendimiento= 64%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,11 (t, 3H), 1,20-1,47 (m, 5H), 1,61-1,68 (m, 1H), 1,79-1,89 (b, 4H), 2,59-2,68 (m, 1H), 3,36 (s, 3H), 3,43-3,50 (m, 4H), 3,54-3,58 (m, 4H), 3,61-3,65 (m, 5H), 7,50 (d, 1H), 7,70 (d, 1H), 8,28 (s, 1H).

MS (m/z) / M+1= 518/520

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I19.9: R_1= ciclohexilo, R_2= metilo, R_3= 4-Cloro-3-[(3-dimetilamino-2-hidroxi-propil)-etil-sulfamoil]-fenilo C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencensulfonamida

Un exceso de epibromhidrina (3 equivalentes molares) reaccionó con I19.5 siguiendo el procedimiento descripto en el ejemplo I19.8. El intermedio se aisló mediante cromatografía sobre gel de sílice eluyendo con una mezcla de ciclohexano/acetato de etilo a una razón de 1/9. A una solución de este intermedio (0,106 mmol, 0,05 g) en EtOH (2 ml) a 50°C, se agregó dimetilamina (0,318 mmol, 0,041 ml) y la mezcla se calentó a 70°C durante 15 h. El solvente luego se removió bajo presión reducida. El residuo se diluyó en agua y se extrajo con diclorometano. La capa orgánica se lavó con agua, se evaporó para dar el producto deseado.

Rendimiento= 64%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,10 (t, 3H), 1,22-1,49 (m, 5H), 1,60-1,70 (m, 1H), 1,79-1,89 (b, 4H), 2,254-2,36 (m, 8H), 2,58-2,66 (m, 1H), 3,31-3,34 (dd, 1H), 3,42-3,60 (m, 6H), 3,79-3,87 (m, 1H), 7,50 (d, 1H), 7,70 (d, 1H), 8,30 (s, 1H).

MS (m/z) / M+1= 516/517

HPLC (pureza uv, λ= 214 nm): 96,60%

Ejemplo I19.10: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-[(2,3-dihidroxi-propil)-etil-sulfamoil]-fenilo

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencensulfonamida

El compuesto del título se preparó como se describió en el ejemplo I19.8 con 3 eq. de 3-bromo-1,2-propano-diol y la mezcla de la reacción se calentó a reflujo durante 12 h. El producto deseado se obtuvo después de la purificación del material crudo mediante cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 3% de metanol.

Rendimiento= 38%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,10 (t, 3H), 1,22-1,49 (m, 5H), 1,62-1,68 (m, 1H), 1,79-1,89 (m, 4H), 2,17-2,22 (m, 1H), 2,59-2,66 (m, 2H), 3,40-3,48 (m, 3H), 3,51-3,57 (dd, 1H), 3,61 (s, 3H), 3,89-3,94 (m, 1H), 7,53 (d, 1H), 7,73 (d, 1H), 8,30 (s, 1H).

MS (m/z) / M+1= 489/490

HPLC (pureza uv, λ= 214 nm): 98,41%

Ejemplo I19.11: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-[etil-(2-hidroxi-3-pirrolidin-1-il-propil)-sulfamoil]-fenilo

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencensulfonamida

El compuesto del título se preparó como se describió en el ejemplo I19.9 usando el mismo intermedio y pirrolidina (3 eq) como nucleófilo. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 2% al 3% de metanol.

Rendimiento= 27%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,10 (t, 3H), 1,19-1,47 (m, 5H), 1,64-1,70 (m, 1H), 1,77-1,90 (m, 4H), 2,48-2,51 (dd, 1H), 2,53-2,78 (m, 7H), 3,33-3,37 (dd, 1H), 3,45-3,54 (m, 2H), 3,56 (d, 2H), 3,61 (s, 3H), 3,87-3,95 (m, 1H), 7,51 (d, 1H), 7,72 (d, 1H), 8,30 (s, 1H).

MS (m/z) / M+1= 542/543

HPLC (pureza uv, λ= 214 nm): 95,50%

Ejemplo I19.12: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-[(2-dietilamino-etil)-etil-sulfamoil]-fenilo

2-Cloro-5-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dietilamino-etil)-N-etil-bencensulfonamida

El compuesto del título se preparó como se describió en el ejemplo I19.8 usando 3,3 eq de carbonato de potasio y 2 eq de clorhidrato de dietilaminoetilcloruro. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con una mezcla de MeOH/DCM (10/90).

Rendimiento= 32%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,00 (t, 6H), 1,17 (t, 3H), 1,22-1,48 (m, 5H), 1,61-1,70 (b, 1H), 1,80-1,90 (m, 4H), 2,48-2,53 (q, 4H), 2,59-2,63 (m, 3H), 3,40-3,45 (m, 4H), 3,63 (s, 3H), 7,50 (d, 1H), 7,72 (d, 1H), 8,30 (s, 1H).

MS (m/z) / M+1= 514/515

HPLC (pureza uv, λ= 214 nm): 99,34%

Ejemplo I19.13: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-[(2-dimetilamino-1-metil-etil)-etil-sulfamoil]-fenilo

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-metil-etil)-N-etil-bencensulfonamida (isómero menor)

y Ejemplo I19.14: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-[(2-dimetilamino-propil)-etil-sulfamoil]-fenilo

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-propil)-N-etil-bencensulfonamida (isómero principal)

Los compuestos del título se prepararon mediante el procedimiento descripto en el ejemplo I19.8 usando 3,3 eq de carbonato de potasio y 2 eq del clorhidrato de 2-dimetilaminoisopropilcloruro.

Los dos "isómeros" se obtuvieron de esta reacción:

El material crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con diclorometano/metanol (99/1) para dar dos isómeros.

El isómero menor:

Rendimiento= 10%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,47 (m, 11H), 1,64-1,72 (m, 1H), 1,77-1,86 (m, 4H), 2,10 (s, 6H), 2,23-2,36 (m, 2H), 2,54-2,66 (m, 1H), 3,31-3,39 (m, 1H), 3,42-3,52 (m, 1H), 3,59 (s, 3H), 3,88-3,93 (m, 1H), 7,50 (d, 1H), 7,70 (d, H), 8,30 (s, 1H).

MS (m/z) / M+1= 500/ 501

HPLC (pureza uv, λ= 214 nm): 98,67%

El isómero principal:

Rendimiento= 30%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 0,92 (d, 3H), 1,11 (t, 3H), 1,23-1,50 (m, 5H), 1,62-1,70 (m, 1H), 1,79-1,89 (m, 4H), 2,14 (s, 6H), 2,59-2,64 (m, 1H), 2,77-2,86 (m, 1H), 3,33-3,51 (m, 4H), 3,59 (s, 3H), 7,50 (d, 1H), 7,70 (d, H), 8,30 (s, 1H).

MS (m/z) / M+1= 500/ 501

HPLC (pureza uv, λ= 214 nm): 99,67%

Ejemplo I20: R_1= ciclohexilo, R_2= acetato de metilo, R_3= clorofenilo

Metil éster del ácido [5-(4-cloro-fenil)-2-ciclohexilimino-[1,3,4]tiadiazol-3-il]-acético

A una solución del 1,3,4-tiadiazol **7h** apropiado (0,34 mmol, 100 mg) en dioxano anhidro (3 ml), se agregó un exceso de bromoacetato de metilo (3,4 mmol). La mezcla resultante se agitó durante 48 h a 90°C. La mezcla se concentró y se agregó una solución saturada de K_2CO_3. La solución se extrajo con acetato de etilo. La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró hasta secarse. El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de solvente ciclohexano/acetato de etilo para dar 66 mg del producto.

Rendimiento= 52%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,35 (m, 5H), 1,55-1,60 (m, 1H), 1,65-1,75 (m, 4H), 2,65 (br, 1H), 3,65 (s, 3H), 4,77 (s, 2H), 7,53 (d, 2H), 7,67 (d, 2H).

MS (m/z) / M+1= 366/368

HPLC (pureza uv, λ= 214nm): 99,70%

Los compuestos de los siguientes ejemplos se prepararon mediante el procedimiento descripto en el ejemplo I20 usando los intermedios y reactivos apropiados:

I20.1	[5-(4-Cloro-fenil)-3-ciclopropilmetil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina
I20.2	3-[5-(4-Cloro-fenil)-2-ciclohexilimino-[1,3,4]tiadiazol-3-il]-propano-1,2-diol
I20.3	[5-(4-Cloro-fenil)-3-(2-dietilamino-etil)-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

Ejemplo I21: R_1= ciclohexilo, R_2= metilo, R_3= metil éster del ácido 3-benzoico

Metil éster del ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

A una solución del 1,3,4-tiadiazol 7 apropiado (1,86 mmol, 590 mg) preparado mediante el procedimiento descripto en el ejemplo 7g en dioxano anhidro (20 ml), se agregaron sulfonato de metiltrifluorometano (2,79 mmol, 316 µl) y trietilamina (2,23 mmol, 310 µl). La mezcla se agitó durante 7h a RT. La mezcla se filtró y el precipitado luego se vertió en una solución diluida de $NaHCO_3$ y se lavó con diclorometano. La capa orgánica se lavó con una solución saturada de NaCl y se secó

sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida para dar 200 mg del producto del título.

Rendimiento: 37%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,35 (m, 5H), 1,45-1,55 (m, 1H), 1,60-1,75 (m, 4H), 2,50-2,60 (m, 1H), 3,45 (s, 3H), 3,80 (s, 3H), 7,55 (t, 1H), 7,80 (d, 2H), 7,95 (d, 2H), 8,10 (s, 1H).

MS (m/z) / M+1= 332,3

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I21.1: R_1= ciclohexilo, R_2= metilo, R_3= ácido 3-benzoico

Ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

A una solución del compuesto I21 (30 mg, 0,09 mmol) en metanol (10 ml) y agua (2,5 ml), se agregó K_2CO_3 (163 mg, 1,17 mmol). La mezcla se calentó a reflujo durante 3 h, se la dejó enfriar y se la concentró en vacío para dar un material crudo. Este residuo se vertió en agua y la suspensión se neutralizó cuidadosamente con una solución de HCl (0,1N) y la fase acuosa se extrajo con acetato de etilo. La capa orgánica se lavó con una solución saturada de NaCl, se secó sobre sulfato de

magnesio, se filtró y se destiló para dar 10 mg del producto del título.

Rendimiento: 35%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,80 (m, 4H), 2,55-2,65 (m, 1H), 3,50 (s, 3H), 7,55 (t, 1H), 7,80 (d, 1H), 7,95 (d, 1H), 8,15 (s, 1H), 13,3 (bs, 1H).

MS (m/z) / M+1= 318,3

HPLC (pureza uv, λ= 214 nm): 99,6%

Ejemplo I21.2: R_1= ciclohexilo, R_2= metilo, R_3= 3-benzamida

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

A una solución de LiOH monohidratado (96 mg, 2,26 mmol) en 1,6 ml de agua, se agregó una solución de I21 (500 mg, 1,51 mmol) en tetrahidrofurano (THF)/MeOH (50/50) (8 ml). La mezcla se agitó a RT durante 24 h y luego se concentró bajo presión reducida. El residuo crudo se disolvió en agua y se agregó una solución de HCl (0,1 N, 38 ml). La mezcla resultante se agitó durante 2 horas. Después de la destilación del agua, el producto se secó sobre P_2O_5 en vacío. A una solución de este material crudo (1,51 mmol) en tolueno (10 ml), se agregó cloruro de tionilo (10 ml) gota a gota y la mezcla se calentó

a reflujo durante 5 h. La mezcla se concentró bajo presión reducida. Una solución de amoníaco (1 ml al 28%) se agregó a una solución del residuo (150 mg, 0,32 mmol) en THF (2 ml) enfriado a 10°C. Después de 3 horas a RT, la mezcla se concentró hasta secarse, se vertió en agua y se extrajo con acetato de etilo. Los extractos orgánicos combinados se lavaron con agua y con una solución saturada de NaCl, se secaron sobre sulfato de magnesio, se filtraron y se destilaron bajo presión reducida. El material sólido blanco se purificó por cromatografía sobre gel de sílice (eluido con diclorometano/metanol a 99/1) para dar 14 mg del producto del título.

Rendimiento: 14%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,45 (m, 5H), 1,60-1,70 (m, 1H), 1,75-1,90 (m, 4H), 2,65-2,75 (m, 1H), 3,60 (s, 3H), 7,52 (s, 1H), 7,60 (dd, 1H), 7,85 (d, 1H), 7,98 (d, 1H), 8,15 (s, 1H), 8,18 (s, 1H).

MS (m/z) / M+1= 317

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I21.3: R_1= ciclohexilo, R_2= metilo, R_3= 3-[N-(2-hidroxi-etil)]-benzamida

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-hidroxi-etil)-benzamida

A una solución de LiOH monohidratado (96 mg, 2,26 mmol) en 1,6 ml de agua, se agregó una solución de I21 (500 mg, 1,51 mmol) en THF/MeOH (50/50) (8 ml). La mezcla se agitó a RT durante 24 h y luego se concentró bajo presión reducida. El residuo se disolvió en agua y se agregó una solución de HCl (0,1 N, 38 ml). La mezcla resultante se agitó durante 2 horas. Después de la destilación del agua, el producto se secó sobre P_2O_5 en vacío. A una solución de este material crudo (1,51 mmol) en tolueno (10 ml), se agregó cloruro de tionilo (10 ml) gota a gota y la mezcla se calentó a reflujo durante 5 h. La mezcla se concentró bajo presión reducida. A una suspensión de este residuo (150 mg, 0,32 mmol) en THF (2 ml) con trietilamina (90 µl, 0,64 mmol) se agregó etanolamina (20 µl, 0,32 mmol) a 0°C y se agitó a temperatura ambiente durante 4 horas. Se agregó agua en la mezcla y se extrajo con acetato de etilo, se lavó con agua y solución salina, se secó con sulfato de magnesio, se filtró en vacío bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice con un gradiente de diclorometano que contenía del 0% al 2% de metanol para dar 50 mg del producto.

Rendimiento: 43%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,35 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,83 (m, 4H), 2,55-2,75 (m, 1H), 3,30-3,37 (m, 2H),

3,45-3,55 (m, 5H), 4,70 (t, 1H), 7,55 (dd, 1H), 7,80 (d, 1H), 7,90 (d, 1H), 8,05 (s, 1H), 8,60 (t, 1H).

MS (m/z) / M+1= 361

HPLC (pureza uv, λ= 214 nm): 99,7%

Ejemplo 21.4: R_1= ciclohexilo, R_2= metilo, R_3= 2-(N-metil)-benzamida

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida

A una solución de LiOH monohidratado (96 mg, 2,26 mmol) en 1,6 ml de agua, se agregó una solución de I21 (500 mg, 1,51 mmol) en THF/MeOH (50/50) (8 ml). La mezcla se agitó a RT durante 24 h y luego se concentró bajo presión reducida. El residuo se disolvió en agua y se agregó una solución de HCl (0,1 N, 38 ml). La mezcla resultante se agitó durante 2 horas. Después de la destilación del agua, el producto se secó sobre P_2O_5 en vacío. A una solución de este material crudo (1,51 mmol) en tolueno (10 ml), se agregó cloruro de tionilo (10 ml) gota a gota y la mezcla se calentó a reflujo durante 5 h. La mezcla se concentró bajo presión reducida. A una suspensión de este residuo (150 mg, 0,32 mmol) en THF (4 ml) con trietilamina (90 µl, 0,64 mmol) se agregó clorhidrato de metilamina (44 mg, 0,64 mmol) a 0°C y se agitó a temperatura ambiente durante 4 horas.

Se agregó agua en la mezcla y se basificó con una solución de $NaHCO_3$, se extrajo con acetato de etilo, se lavó con agua y solución salina, se secó con sulfato de magnesio, se filtró en vacío bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice con un gradiente de diclorometano que contenía del 0% al 2% de metanol para dar el producto deseado.

Rendimiento: 9%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,60-2,70 (m, 1H), 2,82 (s, 3H), 3,55 (s, 3H), 7,60 (t, 1H), 7,80 (d, 1H), 7,90 (d, 1H), 8,05 (s, 1H), 8,55-8,65 (m, 1H).

MS (m/z) / M+1= 331

HPLC (pureza uv, λ= 214 nm): 96,6%

Ejemplo I22: R_1= ciclohexilo, R_2= metilo, R_3= 3,4-dihidroxifenilo

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2-diol; compuesto con ácido trifluoro metanosulfónico

El compuesto I22 se preparó desde el 1,3,4-tiadiazol 7g mediante el procedimiento descripto en el ejemplo I18 usando los intermedios y reactivos apropiados (protocolo C).

En este caso particular, la mezcla se filtró y el precipitado se lavó con dioxano y dietiléter para dar el compuesto esperado como una sal del ácido trifluorometanosulfónico.

Rendimiento= 54,1%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,53 (m, 5H), 1,64-1,69 (b, 1H), 1,78-1,84 (b, 1H), 2,03-2,10 (b, 2H), 3,19-3,27 (b, 1H), 3,84 (s, 3H), 6,90 (d, 1H), 7,13 (d, 1H), 7,20 (s, 1H), 9,55-9,63 (b, 1H), 9,75-9,81 (b, 1H), 9,96-10,3 (b, 1H).

MS (m/z) / M+1= 306/307

HPLC (pureza uv, λ= 214 nm)= 97,35%

Ejemplo I23: R_1= ciclohexilo, R_2= metilo, R_3= 3,5-dimetoxi-4-hidroxi-fenilo

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,6-dimetoxi-fenol

El compuesto I23 se preparó desde el 1,3,4-tiadiazol 7 apropiado mediante el procedimiento descripto en el ejemplo I18 usando los intermedios y reactivos apropiados (protocolo C). En este caso particular, la mezcla se filtró y el precipitado se lavó con dioxano y dietiléter para dar el compuesto esperado como una sal del ácido trifluorometanosulfónico.

Rendimiento= 13,9%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,12-1,27 (b, 1H), 1,27-1,41 (b, 2H), 1,41-1,54 (b, 2H), 1,63-1,70 (b, 1H), 1,80-1,87 (b, 2H), 2,03-2,11 (b, 2H), 3,17-3,26 (b, 1H), 3,88 (9H, s), 7,06 (s, 2H), 9,38-9,47 (b, 1H), 9,80-9,88 (b, 1H).

MS (m/z) / M+1= 350/351

HPLC (pureza uv, λ= 214 nm)= 96,00%

Los compuestos I23.1 e I23.2 se prepararon mediante el procedimiento descripto en el ejemplo I18 usando los intermedios y reactivos apropiados (protocolo C).

I23.1	6-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-piridin-2-ol
I23.2	5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2,3-triol

Ejemplo I24: R_1= ciclohexilo, R_2= metilo, R_3= 8-hidroxiquinolin-2-ilo

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinolin-8-ol

El compuesto I24 se prepararon desde el 1,3,4-tiadiazol 7 apropiado (procedimiento descripto en el ejemplo 7d) mediante el procedimiento descripto en el ejemplo I18.6. En este caso

particular, la mezcla se filtró y el precipitado se lavó con dioxano y dietiléter para dar el compuesto esperado como una sal del ácido trifluorometanosulfónico.

Rendimiento= 58,1%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,25-1,36 (b, 1H), 1,45-1,67 (b, 4H), 1,74-1,81 (b, 1H), 1,90-1,96 (b, 2H), 2,18-2,22 (b, 2H), 3,40-3,50 (b, 1H), 4,02 (s, 3H), 7,35 (d, 1H), 7,63 (d, 1H), 7,69 (t, 1H), 8,21 (d, 1H), 8,64 (d, 1H), 10,08-10,13 (b, 1H), 10,21-10,28 (b, 1H).

MS (m/z) / M+1= 341/342

HPLC (pureza uv, λ= 214 nm)= 94,88%

Ejemplo I25: R_1= ciclohexilo, R_2= metilo, R_3= 2-pirazilo

Ciclohexil-(3-metil-5-pirazin-2-il-3H-[1,3,4]tiadiazol-2-iliden)-amina

El 1,3,4-tiadiazol **7f** (0,770 mmol, 0,200 g) y sulfonato de metiltrifluorometano (0,924 mmol, 0,104 ml) reaccionaron en dioxano (7 ml). El residuo, obtenido después de la basificación a pH 9-10 con una solución saturada de carbonato de potasio, se sometió a cromatografía sobre gel de sílice, eluyendo con diclorometano que contenía del 0% al 10% de metanol para dar el producto esperado.

Rendimiento= 0,075 g, 35,37%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,43 (b, 5H), 1,56-1,65 (b, 1H), 1,90-2,00 (b, 4H), 2,63-2,70 (b, 1H), 3,56 (s, 3H), 8,67 (s, 2H), 9,12 (s, 1H).

HPLC (pureza uv, λ= 214 nm)= 98,32%

MS (m/z) / M+1= 276/277

Ejemplo I26: R_1= ciclohexilo, R_2= metilo, R_3= (E)-2-(3-hidroxi-4-metoxi-fenil)-vinilo

5-[(E)-2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-vinil-2-metoxi-fenol

Los compuestos I26 se prepararon mediante el procedimiento descripto en el ejemplo I18 usando el intermedio (1,3,4-tiadiazol 7 - procedimiento descripto en el ejemplo 7d) y los reactivos apropiados. El producto deseado se aisló mediante cromatografía sobre gel de sílice eluyendo con diclorometano que contenía del 0% al 7% de metanol.

Rendimiento= 0,025 g, 24,1%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,36 (b, 6H), 1,52-1,59 (b, 1H), 1,66-1,78 (b, 4H), 3,39 (s, 3H), 3,76 (s, 3H), 6,70-6,80 (b, 1H), 6,85-6,97 (b, 2H), 6,97-7,07 (b, 2H), 9,04 (s, 1H).

MS (m/z) / M+1= 346/347

HPLC (pureza uv, λ= 214 nm)= 98,64%

Ejemplo I27: R_1= ciclohexilo, R_2= metilo, R_3= 3-metoxi-4-hidroxi-fenilo

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol

Los compuestos I27 se prepararon mediante el procedimiento descripto en ejemplo I18 usando el intermedio (1,3,4-tiadiazol 7 - procedimiento descripto en el ejemplo 7d) y los reactivos apropiados. El producto deseado se aisló mediante cromatografía sobre gel de sílice (Alltech, 2 g de sílice) eluyendo con ciclohexano que contenía del 0% al 4% de acetato de etilo.

Rendimiento= 0,015 g, 14,2%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,01-1,20 (b, 5H), 1,39-1,44 (b, 1H), 1,53-1,63 (b, 4H), 2,4-2,48 (b, 1H), 3,30 (s, 3H), 3,65 (s, 3H), 6,64 (d, 1H), 6,87 (d, 1H), 7,00 (d, 1H), 9,38-9,43 (b, 1H).

MS (m/z) / M+1= 320/321

HPLC (pureza uv, λ= 214 nm)= 99,08%

Ejemplo I28: R_1= ciclohexilo, R_2= metilo, R_3= quinolin-8-ilo

Ciclohexil-(3-metil-5-quinolin-8-il-3H-[1,3,4]tiadiazol-2-iliden)-amina

Los compuestos I28 se prepararon mediante el procedimiento descripto en ejemplo I18 usando el intermedio (1,3,4-tiadiazol 7 - procedimiento descripto en el ejemplo 7b) y los reactivos apropiados. El residuo se sometió a cromatografía sobre gel de sílice, eluyendo con ciclohexano que contenía del 0% al 20% de AcOEt.

Rendimiento= 41%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,35 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,80 (m, 4H), 2,70-2,80 (m, 1H), 3,45 (s, 3H), 7,55-7,60 (m, 1H), 7,60-7,70 (m, 1H), 7,95-8,05 (m, 1H), 8,35-8,40 (m, 1H), 8,40-8,45 (m, 1H), 8,20-8,80 (m, 1H).

MS (m/z) / M+1= 325,3

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I29: R_1= ciclohexilo, R_2= metilo, R_3= 4-dimetilamino-fenilo

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina

Los compuestos I29 se prepararon mediante el procedimiento descripto en ejemplo I18 usando el intermedio (1,3,4-tiadiazol 7 - procedimiento descripto en el ejemplo 7b) y los reactivos apropiados. El residuo se sometió a cromatografía sobre una

columna de gel de sílice usando ciclohexano/acetato de etilo con una razón de 8/2 como solvente.

Rendimiento= 27%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,35 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,80 (m, 4H), 2,50-2,60 (m, 1H), 3,45 (s, 3H), 6,70 (d, 2H), 7,40 (d, 2H).

MS (m/z) / M+1= 317,3

HPLC (pureza uv, λ= 214 nm): 99,5%

Ejemplo I30: R_1= ciclohexilo, R_2= metilo, R_3= 4-sulfonamido-fenilo

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencensulfonamida

Los compuestos I30 se prepararon mediante el procedimiento descripto en ejemplo I18 usando el intermedio (1,3,4-tiadiazol 7 - procedimiento descripto en el ejemplo 7b) y los reactivos apropiados.

El residuo se sometió a cromatografía sobre una columna de gel de sílice eluyendo con ciclohexano que contenía del 0% al 20% de AcOEt.

Rendimiento= 21%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,35 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,75 (m, 4H), 2,50-2,60 (m, 1H), 3,45 (s, 3H), 7,40 (s, 2H), 7,75 (d, 2H), 7,85 (d, 2H).

MS (m/z) / M+1= 353,2

HPLC (pureza uv, λ= 214 nm): 98,5%

Ejemplo I31: R_1= ciclohexilo, R_2= metilo, R_3= 5-cloroindol-2-ilo

[5-(5-Cloro-1H-indol-2-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina; compuesto con ácido trifluorometanosulfónico

Los compuestos I31 se prepararon mediante el procedimiento descripto en ejemplo I18.6 usando el intermedio (1,3,4-tiadiazol 7 - procedimiento descripto en el ejemplo 7b) y los reactivos apropiados.

En este caso particular, la mezcla se filtró y el precipitado se lavó con acetato de etilo para dar el compuesto esperado como una sal del ácido trifluorometanosulfónico.

Rendimiento: 88%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,55 (m, 5H), 1,60-1,70 (m, 1H), 1,75-1,85 (m, 2H), 1.95-2,10 (m, 2H), 3,10-3,30 (m, 1H),

3,85 (bs, 3H), 7,10-7,15 (m, 1H), 7,15-7,20 (m, 1H), 7,40-7,50 (m, 1H), 7,75 (bs, 1H), 10 (bs, 1H), 12,40 (bs, 1H).

MS (m/z) / M+1= 347,3

HPLC (pureza uv, λ= 214 nm): 95,2%

El compuesto I31.1 se preparó mediante el procedimiento descripto en el ejemplo I31 usando los intermedios y reactivos apropiados:

I31.1	2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico

Ejemplo I32: R_1= ciclohexilo, R_2= metilo, R_3= 3-hidroxi-4-metoxi-fenilo

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico

Los compuestos I32 se prepararon mediante el procedimiento descripto en ejemplo I18.6 usando el intermedio (1,3,4-tiadiazol 7 - procedimiento descripto en el ejemplo 7b) y los reactivos apropiados.

En este caso particular, la mezcla se concentró, se filtró y el precipitado se lavó con acetato de etilo para dar el compuesto esperado como una sal del ácido trifluorometanosulfónico.

Rendimiento: 69%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,05-1,45 (m, 5H), 1,50-1,60 (m, 1H), 1,70-1,80 (m, 2H), 1,90-2,05 (m, 2H), 3,05-3,20 (m, 1H), 3,8 (2s, 6H), 7,00 (d, 1H), 7,15-7,20 (m, 2H), 9,60 (bs, 1H), 9,75 (bs, 1H).

MS (m/z) / M+1= 320,3

HPLC (pureza uv, λ= 214 nm): 98%

Ejemplo I33: R_1= ciclohexilo, R_2= metilo, R_3= 4-hidroxi-fenilo 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico

Los compuestos I33 se prepararon mediante el procedimiento descripto en ejemplo I18.6 usando el intermedio (1,3,4-tiadiazol 7 - procedimiento descripto en el ejemplo 7b) y los reactivos apropiados.

En este caso particular, la mezcla se filtró y el precipitado se lavó con acetato de etilo para dar el compuesto esperado como una sal del ácido trifluorometanosulfónico.

Rendimiento: 95%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,05-1,45 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,75 (m, 2H), 1,90-2,00 (m, 2H), 3,30-3,40 (m, 1H), 3,75 (s, 3H), 6,85 (d, 2H), 7,60 (d, 2H), 9,70 (bd, 1H), 10,25 (bd, 1H).

MS (m/z) / M+1= 290,3

HPLC (pureza uv, λ= 214 nm): 95,6%

Ejemplo I34: R_1= ciclohexilo, R_2= metilo, R_3= 3,4-dimetoxi fenilo

Ciclohexil-[5-(3,4-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

El compuesto I34 se preparó desde el 1,3,4-tiadiazol 7 mediante el procedimiento descripto en el ejemplo I17 (protocolo C) usando los intermedios y reactivos apropiados. El producto deseado se aisló mediante cromatografía sobre gel de sílice eluyendo con ciclohexano que contenía del 0% al 20% de acetato de etilo.

Rendimiento: 28%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,30 (m, 5H), 1,45-1,55 (m, 1H), 1,60-1,75 (m, 4H), 2,45-2,60 (m, 1H), 3,40 (s, 3H), 3,70 (2s, 6H), 6,95 (d, 1H), 7,05 (d, 1H), 7,10 (s, 1H)

MS (m/z) / M+1= 334,3

HPLC (pureza uv, λ= 214 nm): 98,2%

Ejemplo I35: R_1= ciclohexilo, R_2= metilo, R_3= 3-bromo-4-metoxi-fenilo

[5-(3-Bromo-4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amino

El compuesto I35 se preparó desde el 1,3,4-tiadiazol 7e, mediante el procedimiento descripto en el ejemplo I17 (protocolo C) usando los intermedios y reactivos apropiados. El producto deseado se aisló mediante cromatografía sobre gel de sílice eluyendo con ciclohexano que contenía del 0% al 15% de acetato de etilo.

Rendimiento: 13%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,35 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,55-2,65 (m, 1H), 3,50 (s, 3H), 3,90 (s, 3H), 7,20 (d, 1H), 7,60 (d, 1H), 7,85 (s, 1H)

MS (m/z) / M+1= 384,2

HPLC (pureza uv, λ= 214 nm): 95%

Los compuestos de los siguientes ejemplos se prepararon mediante el procedimiento descripto en el ejemplo I35 usando los intermedios y reactivos apropiados.

I35.1	Ciclohexil-[5-(4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina
I35.2	Ciclohexil-(3-metil-5-fenil-3H-[1,3,4]tiadiazol-2-iiden)-amina

Ejemplo I36: R_1= ciclohexilo, R_2= metilo, R_3= 3-hidroxi-fenilo 3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol

El compuesto I36 se preparó desde el 1,3,4-tiadiazol 7, mediante el procedimiento descripto en el ejemplo I17 (protocolo C) usando los intermedios y reactivos apropiados. El producto deseado se sometió a cromatografía sobre una columna de gel de sílice usando un gradiente de ciclohexano/acteto de etilo.

Rendimiento: 14%

^{1}H-NMR (400MHz, DMSO) δ ppm : 1,15-1,40 (m,5H), 1,55-1,65 (m,1H), 1,70-1,85 (m,4H), 2,55-2,65 (m,1H), 3,50 (s,3H), 6,85 (d,1H), 7,00-7,05 (m,2H), 7,25 (t,1H), 9,75 (s,1H)

MS (m/z) / M+1 =290,29

HPLC (pureza uv, λ= 214 nm): 93,9%

Ejemplo I37: R_1= ciclohexilo, R_2= metilo, R_3= metil éster del ácido 4-benzoico

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

El compuesto I37 se preparó desde el 1,3,4-tiadiazol 7, mediante el procedimiento descripto en el ejemplo I17 (protocolo C) usando los intermedios y reactivos apropiados. El producto deseado se sometió a cromatografía sobre una columna de gel de sílice usando un gradiente de ciclohexano/acteto de etilo.

Rendimiento: 47%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,35 (m, 5H), 1,50-1,60 (m, 1H), 1,65-1,75 (m, 4H), 2,50-2,65 (m, 1H), 3,50 (s, 3H), 3,80 (s, 3H), 7,70 (d, 2H), 8,00 (d, 2H).

MS (m/z) / M+1= 332,3

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I37.1: R_1= ciclohexilo, R_2= metilo, R_3= ácido 3-benzoico

Ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

A una solución de 1,3,4-tiadiazol I37 (80 mg, 0,24 mmol) en metanol (10 ml) y agua (2,5 ml), se agregó K_2CO_3 (434 mg, 3,14 mmol). La mezcla se calentó a 65°C durante 3 h luego a RT

durante toda la noche. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo. Este residuo se vertió en agua, la suspensión se neutralizó cuidadosamente con una solución de HCl (0,1N) y la fase acuosa se extrajo con diclorometano. La capa orgánica se lavó con una solución saturada de NaCl, se secó sobre sulfato de magnesio, se filtró y se destiló para dar 40 mg del producto del título.
Rendimiento: 52%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,55-2,70 (m, 1H), 3,55 (s, 3H), 7,75 (d, 2H), 8,00 (d, 2H), 13,15 (bs, 1H).
MS (m/z) / M+1= 318,4
HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I37.2: R_1= ciclohexilo, R_2= metilo, R_3= fenilo de ácido 4-hidroxámico

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-hidroxi-benzamida

A una solución de LiOH monohidratado (37 mg, 0,75 mmol) en 0,8 ml de agua, se agregó una solución del compuesto I37 (250 mg, 0,75 mmol) en THF/MeOH (50/50) (4 ml). La mezcla se agitó a RT durante 24 h y luego se concentró bajo presión reducida. El residuo se disolvió en agua (2 ml) y se agregó una solución de

HCl (0,1N, 15 ml). La mezcla resultante se agitó durante 20 minutos. Después de la destilación del agua, el producto crudo se secó sobre P_2O_5 en vacío. A una solución de 75 mg (0,19 mmol) de este material crudo en tolueno (1 ml), se agregaron un gota de piridina y cloruro de tionilo (70 µl) y reaccionaron a reflujo durante 4H. Los volátiles se removieron bajo presión reducida. A una solución de este residuo en THF anhidro, se agregó O-(trimetilsilil) hidroxilamina (230 µl, 0,47 mmol) con tamices moleculares (3A) y la mezcla de la reacción se agtitó durante 18H a RT. Después de la filtración, el filtrado se concentró bajo presión reducida y el residuo se trató con 1 M solución de HCl, se agitó a RT y luego se basificó con una solución de $NaHCO_3$. La fase acuosa se extrajo con diclorometano. La capa orgánica se lavó con solución salina, se secó sobre sulfato de magnesio, se filtró y se concentró en vacío. El producto del título se aisló mediante HPLC de preparación sobre una fase inversa (HYPERSYL C18) eluyendo con agua que contenía del 5% al 95% de acetonitrilo durante 20 mn.

Rendimiento: 12 mg, 20%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,60-2,70 (m, 1H), 3,50 (s, 3H), 7,65 (d, 2H), 7,85 (d, 2H).

MS (m/z) / M+1= 333,2

HPLC (pureza uv, λ= 214 nm): 94,9%

Ejemplo I37.3: R_1= ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

A una solución de LiOH monohidratado (126 mg, 3,0 mmol) en 0,8 ml de agua, se agregó una solución del compuesto I37 (1,0 g, 3 mmol) en THF/MeOH (50/50) (4 ml). La mezcla se agitó a RT durante 24 h y luego se concentró bajo presión reducida. El residuo se disolvió en agua (8 ml) y se agregó una solución de HCl (0,1N, 60 ml). La mezcla resultante se agitó durante 20 minutos. Después de la destilación del agua, el producto crudo se secó sobre P_2O_5 en vacío. A una solución de 120 mg (0,3 mmol) de este material crudo en 2 ml de tolueno, se agregó cloruro de tionilo (2 ml) gota a gota y la mezcla se calentó a reflujo durante 4H. La mezcla se concentró bajo presión reducida. Se agregó una solución de amoníaco (1 ml al 28%) a una solución del residuo en THF (2 ml) enfriado a 10°C. Después de permitir que esté en reposo durante 5 horas a RT, la mezcla se concentró hasta secarse, se vertió en agua y se extrajo con acetato de etilo. Los extractos combinados se lavaron con agua y con una solución saturada de NaCl, se secaron sobre sulfato de magnesio, se filtraron y se destilaron bajo presión rducida. El material sólido blanco se purificó mediante cromatografía sobre gel de sílice (eluido con diclorometano) para dar 64 mg del producto del título.

Rendimiento: 67%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,45 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,60-2,70 (m, 1H), 3,55 (s, 3H), 7,45(bs, 1H), 7,75 (d, 2H), 7,95 (d, 2H), 8,05 (bs, 1H).

MS (m/z) / M+1= 317,35

HPLC (pureza uv, λ= 214 nm): 99,3%

Ejemplo I37.4: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-(2H-tetrazol-5-il)-benzamida

Sal de clorhidrato de 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2H-tetrazol-5-il)-benzamida

A una solución de LiOH monohidratado (187 mg, 4,5 mmol) en 0,8 ml de agua, se agregó una solución del compuesto I37 (250 mg, 0,75 mmol) en THF/MeOH (50/50) (4 ml). La mezcla se agitó a RT durante 24 h y luego se concentró bajo presión reducida. El residuo se disolvió en agua (2 ml) y se agregó una solución de 0,1 M de HCl para llegar a pH 6-7. Después de la destilación del agua, el material crudo se secó sobre P_2O_5 en vacío. Se agregó una resina de tipo de morfolina (180 mg 0,62 mmol) se agregó a una solución de 450 mg (0,62 mmol) de este material crudo en 15 ml de THF enfriado a -15°C. Luego se agregó isobutilcloroformato (105 (105 µl, 0,8 mmol) y la mezcla se agitó a -15°C durante 1H30 antes del agregado de una

suspensión de amino-1H-tetrazol (80 mg, 0,74 mmol) en THF (10 ml). La mezcla de la reacción se dejó en reposo durante 5 horas a RT y la mezcla se filtró sobre gel de sílice. El filtrado se concentró hasta secarse, y se purificó mediante HPLC preparatoria sobre una fase inversa de C18 (HYPERSYL), eluyendo con agua que contenía del 5% al 95% de acetonitrilo en 20 min para dar 10 mg del producto del título. El compuesto se trató con una solución de etanol/HCl para dar la sal de clorhidrato correspondiente.

Rendimiento: 4%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-2,15 (m, 10H), 3,10-3,30 (m, 1H), 4,00 (bs, 3H), 8,10 (bd, 2H), 8,35 (bd, 2H), 12,70 (bs, 1H).

MS (m/z) / M+1= 385,46

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I37.5: R_1= ciclohexilo, R_2= metilo, R_3= 4-(N-quinolin-8-il)-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro [1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida

A una solución de LiOH monohidratado (794 mg, 19 mmol) en 18 ml de agua, se agregó una solución del compuesto I37 (5,7 g, 17,2 mmol) en THF/MeOH (50/50) (100 ml). La mezcla se agitó a

RT durante 24 h y luego se concentró bajo presión reducida. El residuo se disolvió en agua y se agregó una solución de HCl (0,1N, 361 ml). La mezcla resultante se agitó durante 3h30. Después de la destilación del agua, el producto crudo se secó sobre P_2O_5 en vacío. A una suspensión de 200 mg (0,5 mmol) de este material crudo en CH_2Cl_2/DMF (50/50) (6 ml) se agregó resina de ciclocarbodiimida-N-metilo (1,03 g, 1,5 mmol), 1-hidroxi-7-azabenzotriazol (14 mg, 0,1 mmol), N,Ndiisopropiletilamina (175 µl, 1 mmol), 8-aminoquinolina (145 mg, 1 mmol), tamices moleculares (3A) y la mezcla de la reacción se agitó durante 24 h a RT. Después de la filtración, se agregó resina de metilisocianato y la mezcla se agitó durante otras 24h a RT. La mezcla se filtró, el filtrado se concentró bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 20% de acetato de etilo para dar 10 mg del producto del título.

Rendimiento: 4,5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,40 (m, 5H), 1,60-1,65 (m, 1H), 1,75-1,85 (m, 4H), 2,65-2,75 (m, 1H), 3,55 (s, 3H), 7,65-7,75 (m, 2H), 7,80 (d, 1H), 7,90 (d, 2H), 8,15 (d, 2H), 8,5 (d, 1H), 8,75 (d, 1H), 9,00 (d, 1H), 10,70 (s, 1H).

MS (m/z) / M+1= 444,13

HPLC (pureza uv, λ= 214 nm): 96,4%

Ejemplo I37.6: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-(2,6-dimetoxi-piridin-3-il)-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida

A una solución de LiOH monohidratado (794 mg, 19 mmol) en 18 ml de agua, se agregó una solución del compuesto I37 (5,7 g, 17,2 mmol) en THF/MeOH (50/50) (100 ml). La mezcla se agitó a RT durante 24 h y luego se concentró bajo presión reducida. El residuo se disolvió en agua y se agregó una solución de HCl (0,1N, 361 ml). La mezcla resultante se agitó durante 3h30. Después de la destilación del agua, el producto crudo se secó sobre P_2O_5 en vacío. A una suspensión de 200 mg (0,5 mmol) de este material crudo en CH_2Cl_2/DMF (50/50) (6 ml) se agregó resina de ciclocarbodiimida-N-metilo (1,03 g, 1,5 mmol), 1-hidroxi-7-azabenzotriazol (14 mg, 0,1 mmol), N,Ndiisopropiletilamina (260 µl, 1,5 mmol), monoclorohidrato de 3-amino-2,6-dimetoxipiridina (190 mg, 1 mmol), tamices moleculares (3A) y la mezcla de la reacción se agitó durante 24 h a RT. Después de la filtración, se agregó resina de metilisocianato (1 g, 1 mmol) al filtrado y la mezcla se agitó durante otras 24h a RT. La mezcla se filtró, el filtrado se concentró bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un

gradiente de ciclohexano que contenía del 0% al 10% de acetato de etilo para dar 60 mg del producto del título.

Rendimiento: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,35 (m, 5H), 1,50-1,60 (m, 1H), 1,70-1,80 (m, 4H), 2,55-2,65 (m, 1H), 3,50 (s, 3H), 3,85 (s, 3H), 3,90 (s, 3H), 6,35 (d, 1H), 7,70-7,80 (m, 3H), 8,00 (d, 2H), 9,65 (s, 1H).

MS (m/z) / M+1= 454

HPLC (pureza uv, λ = 214 nm): 99,9%

Ejemplo I37.7: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-isopropil-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida

A una solución de LiOH monohidratado (794 mg, 19 mmol) en 18 ml de agua, se agregó una solución del compuesto I37 (5,7 g, 17,2 mmol) en THF/MeOH (50/50) (100 ml). La mezcla se agitó a RT durante 24 h y luego se concentró bajo presión reducida. El residuo se disolvió en agua y se agregó una solución de HCl (0,1N, 361 ml). La mezcla resultante se agitó durante 3h30. Después de la destilación del agua, el producto crudo se secó sobre P_2O_5 en vacío. A una suspensión de 200 mg (0,5 mmol) de este material crudo en CH_2Cl_2/DMF (50/50) (6 ml) se agregó

resina de ciclocarbodiimida-N-metilo (1,03 g, 1,5 mmol), 1-hidroxi-7-azabenzotriazol (15 mg, 0,1 mmol), N,Ndiisopropiletilamina (175 µl, 1 mmol), isopropilamina (85 µl, 1 mmol), tamices moleculares (3A) y la mezcla de la reacción se agitó durante 24 h a RT. Después de la filtración, se agregó resina de metilisocianato (1 g, 1 mmol) al filtrado y la mezcla se agitó durante otras 24h a RT. La mezcla se filtró, el filtrado se concentró bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 20% de acetato de etilo para dar 40 mg del producto del título.

Rendimiento: 22%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 11H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,60-2,70 (m, 1H), 3,55 (s, 3H), 4,05-4,15 (m, 1H), 7,70 (d, 2H), 7,90 (d, 2H), 8,30 (d, 1H).

MS (m/z) / M+1= 359

HPLC (pureza uv, λ = 214 nm): 99,9%

Ejemplo I37.8: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-etil-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida

A una solución de 2M etilamina (1,8 ml, 3,6 mmol) en dicloroetano (5 ml) bajo nitrógeno a 0°C, se agregó 2M de trimetilaluminio (1,8 ml, 3,6 mmol) y la mezcla se agitó a Rt durante 15 minutos. Luego, se agregó una solución del compuesto I37 (180 mg, 0,54 mmol) en dicloroetano (5 ml) y la mezcla de la reacción se dejó agitar durante 48 h a RT. Se agregaron una solución de 2M de etilamina (0,8 ml, 1,6 mmol) y de 2M de trietilaluminio (0,8 ml, 1,6 mmol) para permitir que la reacción se completara y la mezcla se agitó a RT durante otras 24 h. La mezcla se diluyó con 50 ml de diclorometano y 30 ml de agua, se agitó durante 2h, y se filtró a través de Celita. El filtrado se lavó con agua, solución salina y la capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo se sometió a cromatografía rápida eluyendo con un gradiente de ciclohexano que contenía del 0% al 20% de acetato de etilo para lograr 60 ng del compuesto del título.

Rendimiento: 32%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20 (t, 3H), 1,20-1,50 (m, 5H), 1,60-1,70 (m, 1H), 1,80-1,95 (m, 4H), 2,70-2,80 (m, 1H), 3,35-3,45 (m, 2H), 3,65 (s, 3H), 7,90 (d, 2H), 8,05 (d, 2H), 8,65 (m, 1H).

MS (m/z) / M+1= 344,7

HPLC (pureza uv, λ = 214 nm): 99,9%

Ejemplo I37.8-1: R_1= ciclohexilo, R_2= metilo, R_3= 4-(1-etil-1H-tetrazol-5-il)-fenilo

Ciclohexil-{5-[4-(1-etil-1H-tetrazol-5-il)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-amina

A una solución de I37.8 (0,29 mmol, 100 mg) en acetonitrilo (3 ml) a 0°C bajo una atmósfera de nitrógeno, se agregaron azida de sodio (0,44 mmol, 28 mg) y anhidro trifluorometanosulfónico (0,44 mmol, 73 µl). Luego, se agregó la mezcla se agitó toda la noche a temperatura ambiente y una solución saturada de $NaHCO_3$ a pH=7. La capa acuosa se extrajo con diclorometano y la capa orgánica se lavó con agua, solución salina, se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice, eluyendo con un gradiente de diclorometano/metanol, luego mediante HPLC (columna de HYPERSYL de C_{18}), eluyendo con agua que contenía del 5% al 95% de acetonitrilo en 20 minutos para dar el producto del título.

Rendimiento: 9%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,40 (m, 5H), 1,47 (t, 3H), 1,55-1,65 (m, 1H), 1,70-1,82 (m, 4H), 2,50-2,55 (m, 1H), 3,55 (s, 3H), 4,52 (q, 2H), 7,85-7,90 (m, 4H).

MS (m/z) / M+1= 370

HPLC (pureza uv, λ = 214 nm)= 96,8%

Ejemplo I37.9: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-(2-dimetilamino-etil)-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida

A una solución de N,N-dimetiletilendiamina (335 µl, 3 mmol) en dicloroetano (5 ml) bajo una atmósfera de nitrógeno a 0°C, se agregó 2M trimetilaluminio (1,5 ml, 3 mmol) y la mezcla se agitó a RT durante 1h30. Luego, se agregó una solución del compuesto I37 (180 mg, 0,54 mmol) en dicloroetano (5 ml) y la mezcla de la reacción se dejó agitar durante 24 h a RT y 24 h a 45°C. La mezcla se diluyó con 10 ml de diclorometano y 20 ml de agua, se agitó durante 1h30, y se filtró a través de Celita. El filtrado se lavó con agua, solución salina y la capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo se sometió a cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 5% de metanol para dar 140 mg del producto del título.

Rendimiento: 60%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,25 (s, 6H), 2,60-2,70 (m, 1H), 3,55 (s, 3H), 7,75 (d, 2H), 7,90 (d, 2H), 8,50 (m, 1H)

MS (m/z) / M+1= 388

HPLC (pureza uv, λ = 214 nm): 99,4%

Ejemplo I37.10: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-piridin-4-ilmetil-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida

A una solución de LiOH monohidratado (794 mg, 19 mmol) en 18 ml de agua, se agregó una solución del compuesto I37 (5,7 g, 17,2 mmol) en THF/MeOH (50/50) (100 ml). La mezcla se agitó a RT durante 24 h y luego se concentró bajo presión reducida. El residuo se disolvió en agua y se agregó una solución de HCl (0,1N, 361 ml). La mezcla resultante se agitó durante 3h30. Después de la destilación del agua, el producto crudo se secó sobre P_2O_5 en vacío. A una suspensión de 200 mg (0,5 mmol) de este material crudo en CH_2Cl_2/DMF (50/50) (6 ml) se agregó resina de ciclocarbodiimida-N-metilo (1,03 g, 1,5 mmol), 1-hidroxi-7-azabenzotriazol (15 mg, 0,1 mmol), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (38 mg, 0,1 mmol), N,Ndiisopropiletilamina (175 µl, 1 mmol), 4-picolilamina (105 µl, 1 mmol), tamices moleculares (3A) y la mezcla de la reacción se agitó durante 3 días a RT. Esta mezcla se filtró, y en la capa orgánica se agregó resina de metilisocianato (1 g, 1 mmol) y se agitó durante 3 días a RT.

Después de la filtración, el filtrado se concentró bajo presión reducida. El sólido se vertió en agua y la mezcla se agitó durante 1 h, antes de la extracción con diclorometano. La capa orgánica se secó bajo $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 5% de metanol para dar 30 mg del producto del título.

Rendimiento: 15%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,60-2,75 (m, 1H), 3,55 (s, 3H), 4,50 (d, 2H), 7,35 (d, 2H), 7,75 (d, 2H), 8,00 (d, 2H), 8,50 (d, 2H), 9,25 (m, 1H).

MS (m/z) / M+1= 408

HPLC (pureza uv, λ = 214 nm): 99,7%

Ejemplo I37.11: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-metil-N-(1-metil-piperidin-4-il)-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-N-(1-metil-piperidin-4-il)-benzamida

A una solución de I37.1 (0,35 mmol, 200 mg) en DMF (2,5 ml), se agregaron etil-diisopropil-amina (1,6 mmol, 190 µl), hexafluorofosfato de benzotriazol-1-

iloxitris(dimetilamino)fosfonio (0,6 mmol, 265 mg), 1-hidroxi-7-azabenzotriazol (0,25 mmol, 34 mg) y 1-metil-4-(metilamino)piperidina (0,6 mmol, 87 µl) y la mezcla de la reacción se agitó a temperatura ambiente toda la noche. El solvente se destiló bajo presión reducida y el residuo se vertió en agua antes de la extracción con diclorometano. La capa orgánica se lavó con solución salina y luego con una solución saturada de $NaHCO_3$, se secó sobre sulfato de magnesio, se filtró y se concentró bajo vacío. El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 15% de metanol, para dar el producto deseado.

Rendimiento: 93,5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,23-1,45 (m, 5H), 1,55-1,65 (m, 1H), 1,68-1,85 (m, 6H), 1,85-2,00 (m, 2H), 2,23-2,44 (m, 5H), 2,55-2,65 (m, 1H), 2,83 (s, 3H), 3,00-3,10 (m, 2H), 3,55 (s, 3H), 3,85-4,03 (m, 1H), 7,48 (dd, 2H), 7,70 (dd, 2H).

MS (m/z) / M+1= 428

HPLC (pureza uv, λ = 214 nm)= 99,4%

Ejemplo I37.12: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-isobutil-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isobutil-benzamida

A una solución de I37.1 (0,35 mmol, 200 mg) en DMF (2,5 ml) se agregaron etil-diisopropil-amina (1,6 mmol, 190 µl), hexafluorofosfato de benzotriazol-1-iloxitris(dimetilamino)fosfonio (0,6 mmol, 265 mg), 1-hidroxi-7-azabenzotriazol (0,25 mmol, 34 mg) e isobutilamina (2,3 mmol, 80 µl) y la mezcla de la reacción se agitó a temperatura ambiente toda la noche. El solvente se destiló y el residuo se vertió en agua antes de la extracción con diclorometano. La capa orgánica se lavó con solución salina, una solución saturada de $NaHCO_3$, se secó sobre sulfato de magnesio, se filtró y se conventró bajo presión reducida para dar el producto deseado.

Rendimiento: 86%

^{1}H-NMR (400MHz, DMSO) δ ppm: 0,90 (d, 6H), 1,20-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,72-1,90 (m, 5H), 2,60-2,70 (m, 1H), 3,10 (t, 2H), 3,55 (s, 3H), 7,72 (dd, 2H), 7,92 (dd, 2H), 8,55 (t, 1H).

MS (m/z) / M+1= 373

HPLC (pureza uv, λ = 214 nm)= 98,4%

Ejemplo I37.13: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-metil-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida

A una solución de I37.1 (4,25 mmol, 1,7 g) en DMF (20,5 ml) se agregaron N-etildiisopropilamina-N,N-diisopropiletilamina (13,6 mmol, 1,615 ml), hexafluorofosfato de benzotriazol-1-iloxitris(dimetilamino)fosfonio (5,1 mmol, 2,265 mg), 1-hidroxi-7-azabenzotriazol (2,125 mmol, 290 mg) y una solución de metilamina a [2N] en metanol (5,1 mmol, 3,55 ml). La mezcla se agitó a temperatura ambiente toda la noche. La mezcla estuvo en vacío bajo presión reducida, se extrajo con diclorometano en agua. La capa orgánica se lavó con solución salina, una solución saturada de $NaHCO_3$, se secó sobre sulfato de magnesio, y estuvo en vacío bajo presión reducida. El residuo se purificó por cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 4% de metanol, para dar un residuo que se agitó en dietiléter durante una hora. El precipitado se filtró y se secó bajo vacío sobre P_2O_5 para dr 550 mg del producto deseado.

Rendimiento: 44%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,18-1,45 (m, 5H), 1,55-1,68 (m, 1H), 1,68-1,83 (m, 4H), 2,60-2,70 (m, 1H), 2,80 (d, 3H), 3,55 (s, 3H), 7,82 (dd, 2H), 7,92 (dd, 2H), 8,55 (q, 1H).

MS (m/z) / M+1= 331

HPLC (pureza uv, λ= 214 nm)= 99,9%

Ejemplo I37.13-1: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-(2-dimetilamino-etil)-N-metil-benzamida

4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-N-metil-benzamida

A una suspensión de I37.13 (0,3 mmol, 100 mg) en dimetilformamida (1 ml), se agregaron hidruro de sodio en una dispersión al 60% en aceite mineral (0,6 mmol, 24 mg), clorhidrato de dimetilaminoetilcloruro (0,36 mmol, 52 mg) y K_2CO_3 (0,36 mmol, 50 mg). La mezcla se agitó toda la noche a 40°C. Luego, se agregó terc-butóxido de potasio (0,18 mmol, 20 mg) y la mezcla se agitó durante 24 h. Se agregaron clorhidrato de 2-dimetilaminoetilcloruro (0,18 mmol, 26 mg) y K_2CO_3 (0,18 mmol, 25 mg) y se calentaron a 40°C toda la noche. La mezcla se redujo bajo vacío a presión para dar un residuo que se purificó por cromatografía sobre gel de sílice, eluyendo con un gradiente de diclorometano que contenía del 0% al 6% de metanol para dar el producto del título.

Rendimiento: 16%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,42 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,00 (s, 3H), 2,25 (s, 3H), 2,30-2,40 (m, 1H), 2,60-2,70 (m, 1H), 2,88-3,02 (m, 3H), 3,55 (s, 3H), 7,45 (dd, 2H), 7,70 (dd, 2H).

MS (m/z) / M+1= 402

HPLC (pureza uv, λ = 214 nm)= 98,8%

Ejemplo I37.14: R_1= ciclohexilo, R_2= metilo, R_3= 4-(3-hidroximetil-piperidin-1-carbonil)-fenilo

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-1-(3-hidroximetil-piperidin-1-il)-metanona

El compuesto I37.14 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I37.1 como material inicial. El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 5% de metanol, para dar el producto deseado.

Rendimiento: 34%

^{1}H-NMR (350K, 400MHz, DMSO) δ ppm: 1,20-1,50 (m, 7H), 1,50-1,70 (m, 3H), 1,70-1,85 (m, 5H), 2,63-2,78 (m, 2H), 2,88-2,98 (m, 1H), 3,18-3,28 (m, 1H), 3,28-3,38 (m, 1H), 3,50 (s, 3H), 3,75-4,10 (m, 2H), 4,18-4,28 (m, 1H), 7,45 (dd, 2H), 7,68 (dd, 2H).

MS (m/z) / M+1= 415

HPLC (pureza uv, λ= 214 nm)= 95,4%

Ejemplo I37.15: R_1= ciclohexilo, R_2= metilo, R_3= 4-[N-[(S)-1-terc-butoxicarbonil-2-(4-hidroxi-fenil)-etil]}benzamida

terc-Butil éster del ácido 2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico

El compuesto I37.15 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I37.1 como material inicial. El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 2% de metanol y luego el producto se lavó con agua, se extrajo con acetato de etilo y la capa orgánica se lavó con solución salina, se secó sobre sulfato de magnesio y se redujo bajo vacío bajo presión, para dar el producto del título.

Rendimiento: 70%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,40 (m, 14H), 1,55-1,65 (m, 1H), 1,70-1,80 (m, 4H), 2,58-2,68 (m, 1H), 2,91-3,01 (m, 2H), 3,52 (s, 3H), 4,45-4,51 (m, 1H), 6,65 (dd, 2H), 7,08 (dd, 2H), 7,71 (dd, 2H), 7,90 (dd, 2H), 8,75 (d, 1H), 9,15 (s, 1H).

MS (m/z) / M+1= 537

HPLC (pureza uv, λ= 214 nm)= 96,3%

Ejemplo I37.15-a: R_1= ciclohexilo, R_2= metilo, R_3= 4-[N-((S)-1-carboxi-2-(4-hidroxi-fenil)-etil)]benzamida

Ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico; compuesto con ácido 2,2,2-trifluoro-acético

A una solución de I37.15 (0,186 mmol, 100 mg) en diclorometano (1,5 ml), se agregó ácido trifluoroacético (4,4 mmol, 378 µl) y la mezcla se agitó a reflujo durante 2 horas. La mezcla se purificó mediante cromatografía sobre gel de sílice, eluyendo con un gradiente de diclorometano que contenía del 0% al 10% de metanol para dar 60 mg del producto del título.

Rendimiento: 54%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,12-1,52 (m, 5H), 1,58-1,68 (m, 1H), 1,73-1,85 (m, 2H), 1,85-2,05 (m, 2H), 2,88-3,11 (m, 3H), 3,75 (s, 3H), 4,48-4,60 (m, 1H), 6,62 (dd, 2H), 7,08 (dd, 2H), 7,85 (dd, 2H), 7,95 (dd, 2H), 9,15 (s, 1H), 12,75 (s, 1H).

MS (m/z) / M+1= 481

HPLC (pureza uv, λ= 214 nm)= 98%

Ejemplo I37.16: R_1= ciclohexilo, R_2= metilo, R_3= 4-(N-((S)-1-terc-butoxicarbonil)-etil)benzamida

terc-Butil éster del ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-propiónico

El compuesto I37.16 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I37.1 como un material inicial.

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 2% de metanol y el producto se lavó con agua, se filtró y se secó bajo vacío a presión con P_2O_5 para dar el compuesto del título.

Rendimiento: 65%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,40 (m, 17H), 1,55-1,65 (m, 1H), 1,70-1,82 (m, 4H), 2,58-2,68 (m, 1H), 3,52 (s, 3H), 4,35 (q, 1H), 7,73 (dd, 2H), 7,95 (dd, 2H), 8,75 (d, 1H).

MS (m/z) / M+1= 445

HPLC (pureza uv, λ= 214 nm)= 99,3%

Ejemplo I37.16-a: R_1= ciclohexilo, R_2= metilo, R_3= 4-(N-((S)-1-carboxi)-etil)benzamida

Ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-propiónico; compuesto con ácido 2,2,2-trifluoro-acético

A una solución de I37.16 (0,225 mmol, 100 mg) en diclorometano (1 ml) a 0°C, se agregó ácido trifluoroacético (5,85 mmol, 457 µl) y la mezcla se agitó a temperatura ambiente toda la noche. La mezcla se purificó mediante cromatografía sobre gel de sílice, eluyendo con un gradiente de diclorometano que contenía del 0% al 5% de metanol para dar 40 mg del producto del título.

Rendimiento: 35%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,48 (m, 8H), 1,55-1,65 (m, 1H), 1,70-1,81 (m, 2H), 1,81-2,00 (m, 2H), 2,89-3,05 (m, 1H), 3,71 (s,3H), 4,44 (q, 1H), 7,87 (dd, 2H), 8,03 (dd, 2H), 8,82 (d, 1H), 12,57 (s, 1H).

MS (m/z) / M+1= 388/389

HPLC (pureza uv, λ= 214 nm)= 97,9%

Ejemplo I37.17: R_1= ciclohexilo, R_2= metilo, R_3= 4-(4-piridin-2-il-piperazin-1-carbonil)-fenilo

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-piridin-2-il-piperazin-1-il)-metanona

El compuesto I37.17 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I37.1 como un material inicial.

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 5% de metanol y luego el producto se lavó con agua, se filtró y se secó bajo presión reducida sobre P_2O_5 para dar el producto deseado.

Rendimiento: 82%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,48 (m, 5H), 1,55-1,65 (m, 1H), 1,70-2,00 (m, 4H), 2,62-2,92 (m, 1H), 3,35-3,87 (m, 11H),

6,67 (dd, 1H), 6,88 (d, 1H), 7,45-7,63 (m, 3H), 7,78 (dd, 2H), 8,12 (d, 1H).

MS (m/z) / M+1= 463

HPLC (pureza uv, λ = 214 nm)= 99,9%

Ejemplo I37.18: R_1= ciclohexilo, R_2= metilo, R_3= 4-[4-(4-fluoro-fenil)-piperazin-1-carbonil]-fenilo

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-[4-(4-fluoro-fenil)-piperazin-1-il]-metanona

El compuesto I37.18 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I37.1 como un material inicial.

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 5% de metanol y luego el producto se lavó con agua, se filtró y se secó bajo presión reducida sobre P_2O_5 para dar el producto deseado.

Rendimiento: 31%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,65-1,86 (m, 4H), 2,56-2,70 (m, 1H), 2,96-3,10 (m, 4H), 3,37-3,85 (m, 7H), 6,67 (dd, 1H), 6,92-7,12 (m, 4H), 7,51 (dd, 2H), 7,71 (dd, 2H).

MS (m/z) / M+1= 480

HPLC (pureza uv, λ= 214 nm)= 98,6%

Ejemplo I37.19: R_1= ciclohexilo, R_2= metilo, R_3= 4-[N-(3,4,5-trimetoxi-bencil)]-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida

El compuesto I37.19 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I37.1 como un material inicial.

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de ciclohexano que contenía del 0% al 30% de acetato de etilo, para dar un producto que se lavó con agua, se filtró y se secó bajo presión reducida sobre P_2O_5 para dar el producto deseado.

Rendimiento: 52%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,19-1,42 (m, 5H), 1,55-1,65 (m, 1H), 1,71-1,88 (m, 4H), 2,60-2,70 (m, 1H), 3,50-3,55 (m, 3H), 3,55 (s, 3H), 3,75 (s, 6H), 4,42 (d, 2H), 6,65 (s, 4H), 7,70-7,80 (m, 1H), 8,00 (d, 1H), 9,10 (t, 1H).

MS (m/z) / M+1= 497

HPLC (pureza uv, λ= 214 nm)= 99,5%

Ejemplo I37.20: R_1= ciclohexilo, R_2= metilo, R_3= 4-(4-pirimidin-2-il-piperazin-1-carbonil)-fenilo

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-pirimidin-2-il-piperazin-1-il)-metanona

El compuesto I37.20 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I37.1 como un material inicial.

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 1% de metanol, para dar un producto que se lavó con agua, se filtró y se secó bajo presión reducida sobre P_2O_5 para dar el producto deseado.

Rendimiento: 48%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,41 (m, 5H), 1,55-1,65 (m, 1H), 1,68-1,75 (m, 4H), 2,55-2,70 (m, 1H), 3,00-3,90 (m, 11H), 6,65 (t, 1H), 6,88 (d, 1H), 7,50 (dd, 2H), 7,70 (dd, 2H), 8,38 (d, 2H).

MS (m/z) / M+1= 464

HPLC (pureza uv, λ= 214 nm)= 97%

Ejemplo I37.21: R_1= ciclohexilo, R_2= metilo, R_3= 4-(4-metil-piperazin-1-carbonil)-fenilo

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-metil-piperazin-1-il)-metanona

El compuesto I37.21 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I37.1 como un material inicial.

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 10% de metanol, para dar un producto que se lavó con agua, se filtró y se secó bajo presión reducida sobre P_2O_5 para dar el producto deseado.

Rendimiento: 55%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,18-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,69-1,81 (m, 4H), 2,25 (s, 3H), 2,33-2,52 (m, 4H), 2,59-2,69 (m, 1H), 3,25-3,45 (m, 2H), 3,52 (s, 3H), 3,55-3,70 (m, 2H), 7,78 (dd, 2H), 7,71 (dd, 2H).

MS (m/z) / M+1= 400

HPLC (pureza uv, λ= 214 nm)= 99,6%

Ejemplo I37.22: R_1= ciclohexilo, R_2= metilo, R_3= 4-[N-(3-(4-metil-piperazin-1-il)-pripil)]benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida

El compuesto I37.22 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I37.1 como un material inicial.

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 10% de metanol, para dar un producto que se agitó en dietiléter, se filtró y se secó bajo presión reducida sobre P_2O_5 para dar el producto deseado.

Rendimiento: 3,5%

^{1}H-NMR (400MHz, CDCl^3): δ ppm: 1,20-1,50 (m, 5H), 1,60-2,05 (m, 7H), 2,35 (s, 3H), 2,48-2,85 (m, 11H), 3,52-3,64 (m, 2H), 3,50 (s, 3H), 7,68 (dd, 2H), 7,87 (dd, 2H), 8,00-8,08 (m, 1H).

MS (m/z) / M+1= 457

HPLC (pureza uv, λ= 214 nm)= 97,2%

Ejemplo I37.23: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-[(1-etil-pirrolidin-2-ilmetil)-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(1-etil-pirrolidin-2-ilmetil)-benzamida

A una solución de 2-(aminometil)-1-etilpirrolidina (7,5 mmol, 967 mg) en diclorometano (10 ml) bajo una atmósfera de nitrógeno, se agregó gota a gota trimetilaluminio [2N] en tolueno (7,5 mmol, 3,8 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Una solución del compuesto I37 (1,5 mmol, 500 mg) en dicloroetano (10 ml) luego se agregó y la agitación continuó a 65°C toda la noche. A temperatura

ambiente, se agregaron diclorometano (30 ml) y agua (50 ml) y la mezcla se agitó durante varias horas. La mezcla se filtró a través de celita, se extrajo con diclorometano, se lavó con agua y solución salina, se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 10% de metanol para dar el producto deseado.

Rendimiento: 79%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,05 (t, 3H), 1,20-1,42 (m, 5H), 1,55-1,70 (m, 4H), 1,70-1,85 (m, 5H), 2,10-2,18 (m, 1H), 2,25-2,35 (m, 1H), 2,55-2,70 (m, 2H), 2,80-2,90 (m, 1H), 3,00-3,12 (m, 2H), 3,39-3,49 (m, 1H), 3,55 (s, 3H), 7,71 (dd, 2H), 7,92 (dd, 2H), 8,49 (t, 1H).

MS (m/z) / M+1= 428

HPLC (pureza uv, λ= 214 nm)= 99,2%

Ejemplo I37.24: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-[(piridin-2-ilmetil)-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida

El compuesto I37.24 se preparó mediante el procedimiento descripto en el ejemplo I37.23 usando los intermedios y reactivos apropiados (I37 y 2-(aminoetil)piridina).

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 8% de metanol para dar producto deseado.

Rendimiento: 34%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,42 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,60-2,70 (m, 1H), 3,55 (s, 3H), 4,50 (d, 2H), 7,35-7,40 (m, 1H), 7,70-7,80 (m, 3H), 8,00 (dd, 2H), 8,45-8,50 (m, 1H), 8,57 (s, 1H), 9,30 (t, 1H).

MS (m/z) / M+1= 408

HPLC (pureza uv, λ= 214 nm)= 98,6%

Ejemplo I37.25: R_1= ciclohexilo, R_2= metilo, R_3= 4-(N-bencil)-benzamida

N-Bencil-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

El compuesto I37.25 se preparó mediante el procedimiento descripto en el ejemplo I37.23 usando los intermedios y reactivos apropiados (I37 y bencilamina).

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 2% de metanol para dar producto deseado.

Rendimiento: 34%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,65-1,85 (m, 4H), 2,55-2,70 (m, 1H), 3,52 (s, 3H), 4,48 (d, 2H), 7,19-7,39 (m, 5H), 7,72 (dd, 2H), 7,98 (dd, 2H), 9,13 (t, 1H)

MS (m/z) / M+1= 407

HPLC (pureza uv, λ= 214 nm)= 99,2%

Ejemplo I37.26: R_1= ciclohexilo, R_2= metilo, R_3= 4-[N-(1-

242 s/10 3/c 2ª parte 0078

¡Esta página no forma parte del folleto!

WO 02-28847

2/2

Fecha: 11 de abril de 2002

Destino: Agente

Domicilio:

bencil-piperidin-4-il)]-benzamida

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

El compuesto I37.26 se preparó mediante el procedimiento descripto en el ejemplo I37.23 usando los intermedios y reactivos apropiados (I37 y 4-amino-1-bencilpiperidina).
El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 8% de metanol para dar producto deseado.
Rendimiento: 50%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,53-1,65 (m, 3H), 1,70-1,83 (m, 6H), 1,97-2,07 (m, 2H), 2,70-2,80 (m, 1H), 2,77-2,87 (m, 2H), 3,47 (s, 2H), 3,55 (s, 3H), 3,70-3,85 (m, 1H), 7,22-7,35 (m, 5H), 7,70 (dd, 2H), 7,93 (dd, 2H), 8,35 (d, 1H).
MS (m/z) / M+1= 490
HPLC (pureza uv, λ= 214 nm)= 96,4%

Ejemplo I37.27: R_1= ciclohexilo, R_2= metilo, R_3= 4-[N-(2-etil-2H-pirazol-3-il)-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-il)-benzamida

0076β

El compuesto I37.27 se preparó mediante el procedimiento descripto en el ejemplo I37.23 usando los intermedios y reactivos apropiados (I37 y 5-amino-1-etilpirazol).

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 6% de metanol y luego el sólido se agitó en dietiléter durante 15 minutos, se filtró y se secó bajo presión reducida para dar producto del título.

Rendimiento: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,45 (m, 8H), 1,60-1,70 (m, 1H), 1,75-1,87 (m, 4H), 2,63-2,73 (m, 1H), 3,55 (s, 3H), 4,05 (q, 2H), 6,25 (d, 1H), 7,45 (d, 1H), 7,83 (dd, 2H), 8,10 (dd, 2H), 10,40 (s, 1H).

MS (m/z) / M+1= 411

HPLC (pureza uv, λ= 214 nm)= 99,7%

Ejemplo I37.28: R_1= ciclohexilo, R_2= metilo, R_3= 4-(2-morfolin-4-il-etil)-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida

El compuesto I37.28 se preparó mediante el procedimiento descripto en el ejemplo I37.23 usando los intermedios y reactivos apropiados (I37 y N-(2-aminoetil)morfolina).

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 6% de metanol y luego el sólido se agitó en dietiléter durante 15 minutos, se filtró y se secó bajo presión reducida para dar producto del título.

Rendimiento: 21%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,63 (m, 1H), 1,70-1,83 (m, 5H), 2,35-2,50 (m, 6H), 2,57-2,67 (m, 1H), 3,38 (q, 2H), 3,50 (s, 3H), 3,52-3,57 (m, 4H), 7,80 (dd, 2H), 7,90 (dd, 2H), 8,50 (t, 1H)

MS (m/z) / M+1= 430

HPLC (pureza uv, λ= 214 nm)= 99,9%

Ejemplo I37.28-1: R_1= ciclohexilo, R_2= metilo, R_3= 4-[(N-ciano-N'-etilmorfolin)-carboximidamin]-fenilo

[5-(4-((N-ciano-N'-etilmorfolin)-carboximidamido)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

A una solución de I37.28 (2,33 mmol, 1 g) en tolueno (15 ml), se agregó reactivo de Lawesson (4,65 mmol, 1,88 g) y la mezcla

se agitó toda la noche a reflujo. Después de enfriar a temperatura ambiente, la mezcla se acidificó con una solución de HCl al 5% (3,5 ml) luego se basificó con una solución de $NaHCO_3$. La capa acuosa se extrajo con acetato de etilo y las capas orgánicas combinadas se lavaron con agua, solución salina, se secaron sobre sulfato de magnesio, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice para dar 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N(2-morfolin-4-il-etil)tiobenzamida.

Rendimiento: 56%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,83 (m, 4H), 2,60-2,75 (m, 3H), 3,52 (s, 3H), 3,55-3,63 (m, 4H), 3,78 (t, 2H), 3,80-3,90 (m, 2H), 7,70 (dd, 2H), 7,82 (dd, 2H), 10,28 (t, 1H).

A una solución de 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N(2-morfolin-4-il-etil)tiobenzamida (1,12 mmol, 500 mg) en THF (20 ml), se agregó hidruro de sodio (60% de dispersión en aceite mineral, 1,12 mmol, 44 mg) y la mezcla se calentó a reflujo durante una hora. Después de enfriar a temperatura ambiente, se agregó yoduro de metilo (1,35 mmol, 84 µl) y la mezcla se calentó durante 4 horas a reflujo y luego toda la noche a temperatura ambiente. La

mezcla se concentró bajo presión reducida para dar un material crudo que se solubilizó en etanol (50 ml). A esta solución se agregaron cianamida (1,8 mmol, 75 mg) y trietilamina (0,9 mmol, 125 µl) y la mezcla se agitó durante 2 días a reflujo. Se agregaron cloruro de mercurio(II) (1,68 mmol, 457 mg) y cianamida (2,35 mmol, 100 mg) y la reacción se dejó agitar durante 3 días a temperatura ambiente. La mezcla se concentró bajo presión reducida y el residuo se diluyó en acetato de etilo y se filtró a través de celita. El filtrado se concentró bajo vacío. El residuo se cromatografió sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 5% de metanol para dar el compuesto del título.

Rendimento: 17%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,18-1,42 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,40-2,50 (m, 4H), 2,50-2,60 (m, 2H), 2,60-2,70 (m, 1H), 3,45-3,55 (m, 2H), 3,55 (s, 3H), 3,55-3,65(m, 4H), 7,68 (dd, 2H), 7,52 (dd, 2H), 9,15 (t, 1H).

MS (m/z) / M+1= 454

HPLC (pureza uv, λ= 214 nm) = 95%

Ejemplo I37.29: R_1= ciclohexilo, R_2= metilo, R_3= 4-N-(2-pirrolidin-1-il-etil)-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida

El compuesto I37.29 se preparó mediante el procedimiento descripto en el ejemplo I37.23 usando los intermedios y reactivos apropiados (I37 y 1-(2-aminoetil)pirrolidina).

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 14% de metanol para dar producto deseado.

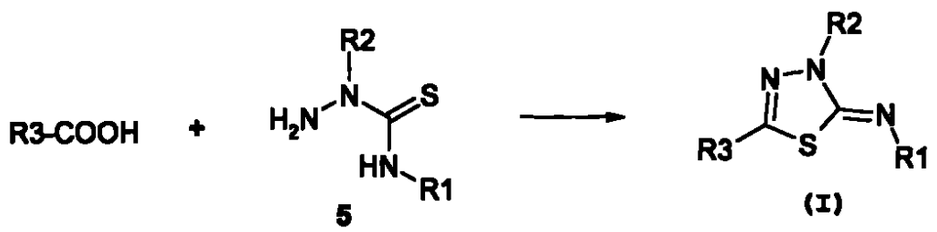
Rendimiento: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,45 (m, 5H), 1,60-1,87 (m, 9H), 2,45-2,70 (m, 7H), 3,35-3,45 (m, 2H), 3,60 (s, 3H), 7,73 (dd, 2H), 7,95 (dd, 2H), 8,55 (t, 1H).

MS (m/z) / M+1= 414

HPLC (pureza uv, λ= 214 nm)= 99,9%

Protocolo D :



EJEMPLO I: PROTOCOLO D

Ejemplo I15: R_1= ciclohexilo, R_2= metilo, R_3= 4-metilsulfonil-fenilo

Ciclohexil-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

A una emzcla de ácido 4-metilsulfonil-benzoico (2,5 mmol, 500 mg), se agregó 5-metiltiosemicarbazida 5a (2,5 mmol, 468 mg) en dioxano anhidro (5 ml) a 65°C, $POCl_3$ (3 mmol, 280 µl) y la mezcla se calentó a 95°C durante 5 horas. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo que se basificó a pH 8-7 con una solución saturada de $NaHCO_3$. La fase acuosa se extrajo con diclorometano. La capa orgánica se lavó con una solución saturada de NaCl, se secó sobre sulfato de magnesio, se filtró y se destiló para dar un residuo que se purificó mediante cromatografía sobre gel de sílice (eluida con un gradiente de ciclohexano/acetato de etilo que terminaba con la razón 80/20) para dar 230 mg del compuesto del título.

Rendimiento: 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,25-1,45 (m, 5H), 1,65-1,75 (m, 1H), 1,75-1,95 (m, 4H), 1,70-1,80 (m, 1H), 3,35 (s, 3H), 3,65 (s, 3H), 8,05 (dd, 4H).

MS (m/z) / M+1= 352,5

HPLC (pureza uv, λ= 214 nm): 95,3%

Los compuestos de los siguientes ejemplos se prepararon mediante el procedimiento descripto en el ejemplo I15 usando los intermedios y reactivos apropiados:

I15.1	[3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina
I15.2	Ciclohexil-[5-(3-metoxi-4-nitro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina

Ejemplo I38: R_1= ciclohexilo, R_2= Me, R_3= 3-piridilo

Ciclohexil-(3-metil-5-piridin-3-il-3H-[1,3,4]tiadiazol-2-iliden]-amina

El compuesto I38 se preparó mediante el procedimiento descripto en el ejemplo I15 (protocolo D) usando los intermedios y reactivos apropiados.

El producto del título se aisló por cromatografía sobre gel de sílice eluyendo con ciclohexano que contenía del 0% al 10% de acetato de etilo.

Rendimiento= 0,06 g, 13,5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,44 (m, 5H), 1,59-1,64 (b, 1H), 1,73-1,83 (b, 4H), 2,61-2,70 (b, 1H), 3,54 (s, 3H), 7,50-7,53 (m, 1H), 8,04 (d, 1H), 8,63-8,67 (m, 1H), 8,85 (s, 1H).

MS (m/z) / M+1= 275/276

HPLC (pureza uv, λ= 214 nm)= 95,87%

Ejemplo I39: R_1= ciclohexilo, R_2= metilo, R_3= 3-sulfamoil-fenilo

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencensulfonamida

El compuesto I39 se preparó mediante el procedimiento descripto en el ejemplo I15 (protocolo D) usando los intermedios y reactivos apropiados.

El producto del título se aisló por cromatografía sobre gel de sílice eluyendo con diclorometano que contenía del 0% al 5% de metanol.

Rendimiento= 8,0%

^{1}H-NMR (400MHz, DMSO) δppm: 1,18-1,41 (m, 5H), 1,58-1,63 (m, 1H), 1,73-1,84 (m, 4H), 2,60-2,67 (m, 1H), 3,56 (s, 3H), 7,48 (s, 2H), 7,67 (t, 1H), 7,82-7,90 (m, 2H), 8,12 (s, 1H).

MS (m/z) / M+1= 353/354

HPLC (pureza, λ= 214 nm)= 97,55%

Ejemplo I40: R_1= ciclohexilo, R_2= metilo, R_3= benzo[1,3]dioxol-5-ilo

(5-Benzo[1,3]dioxol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

El compuesto I40 se preparó mediante el procedimiento descripto en el ejemplo I15 (protocolo D) usando los intermedios y reactivos apropiados.

El producto del título se aisló por cromatografía sobre gel de sílice eluyendo con ciclohexano que contenía del 0% al 15% de acetato de etilo.

Rendimiento= 27%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,45 (m, 5H), 1,60-1,70 (m, 1H), 1,70-1,85 (m, 4H), 2,60-2,70 (m, 1H), 3,50 (s, 3H), 6,15 (s, 2H), 7,00 (d, 1H), 7,15 (d, 1H), 7,25 (s, 1H)

MS (m/z) / M+1= 318

HPLC (pureza uv, λ= 214 nm): 99,9%

Ejemplo I41: R_1= ciclohexilo, R_2= metilo, R_3= 3,4,5-trimetoxifenilo

Ciclohexil-[3-metil-5-(3,4,5-trimetoxi-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina

El compuesto I41 se preparó mediante el procedimiento descripto en el ejemplo I15 (protocolo D) usando los intermedios y reactivos apropiados.

El producto del título se aisló por cromatografía sobre gel de sílice eluyendo con heptano que contenía del 0% al 20% de dietiléter.

Rendimiento= 26%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,50 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,65-2,70 (m, 1H), 3,50 (s, 3H), 3,70 (s, 3H), 3,85 (s, 6H), 6,90 (s, 2H)

MS (m/z) / M+1= 364,49

HPLC (pureza uv, λ= 214 nm): 99,9%

EJEMPLO I: PROTOCOLO A

Ejemplo I42: R_1= ciclohexilo, R_2= metilo, R_3= 4-ciano-fenilo

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo

A una suspensión de perclorato de 1,3,4-tiadiazolio (3c) (0,86 mmol, 300 mg) en etanol (20 ml), se agregaron ciclopentilamina (1,03 mmol, 102 µl) y trietilamina (1,03 mmol, 264 µl), y la mezcla se agitó a reflujo durante toda la noche. La mezcla se

concentró mediante la destilación del solvente y el material crudo se solubilizó en acetato de etilo. Las sales inorgánicas se removieron mediante la extracción con agua. La capa orgánica se lavó con agua y una solución de NaCl, se secó bajo sulfato de magnesio, se filtró y se detiló para dar un residuo que se cromatografió sobre una columna de gel de sílice (usando un gradiente de solvente de acetato de etilo-ciclohexano comenzando con una razón de 0/100 a 20/80) para aislar 210 mg del producto puro.

Rendimiento= 85,7%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,40-1,95 (m, 8H), 3,15-3,25 (m, 1H), 3,50 (s, 3H), 7,80 (dd, 2H), 7,92 (dd, 2H).

MS (m/z) / M+1= 285

Ejemplo I43: R_1= ciclohexilo, R_2= metilo, R_3= 4-cianofenilo

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo

El compuesto I43 se preparó mediante el procedimiento descripto en el ejemplo I42 usando los intermedios y reactivos apropiados (protocolo A). El residuo se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 20% de acetato de etilo.

Rendimiento= 70,6%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,40-1,85 (m, 12H), 2,75-2,85 (m, 1H), 3,50 (s, 3H), 7,80 (dd, 2H), 7,90 (dd, 2H).
MS (m/z) / M+1= 313

Ejemplo I44: R_1= 4-fluorofenilo, R_2= metilo, R_3= 4-ciano-fenilo
4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

El compuesto I44 se preparó mediante el procedimiento descripto en el ejemplo I42 usando los intermedios y reactivos apropiados (protocolo A). El residuo se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 20% de acetato de etilo.
Rendimiento= 71,1%
^{1}H-NMR (400MHz, DMSO) δ ppm: 3,72 (s, 3H), 7,03-7,10 (m, 2H), 7,16-7,25 (m, 2H), 7,83 (dd, 2H), 7,93 (dd, 2H).
MS (m/z) / M+1= 311

Ejemplo I45: R_1= 3-fenol, R_2= metilo, R_3= 4-ciano-fenilo
4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

El compuesto I45 se preparó mediante el procedimiento descripto en el ejemplo I42 usando los intermedios y reactivos apropiados (protocolo A). El residuo se purificó por

cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 20% de metanol.

Rendimiento= 99%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,70 (s, 3H), 6,41-6,55 (m, 3H), 7,15 (t, 1H), 7,82 (dd, 2H), 7,91 (dd,2H), 9,42 (s, 1H).

MS (m/z) / M+1= 309

Ejemplo I46: R_1= ácido 4-fluoro-3-benzoico, R_2= metilo, R_3= 4-ciano-fenilo

Ácido 5-[5-(4-Ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico

El compuesto I46 se preparó mediante el procedimiento descripto en el ejemplo I42 usando los intermedios y reactivos apropiados (protocolo A). En este caso particular el residuo se precipitó en acetato de etilo para dar el producto puro.

Rendimiento= 65,5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,74 (s, 3H), 7,24-7,37 (m, 3H), 7,44-7,51 (m, 1H), 7,85 (dd, 2H), 7,94 (dd,2H), 13,31 (b, 1H).

MS (m/z) / M+1= 355

Ejemplo I47: R_1= 4-metil-ciclohexilo, R_2= metilo, R_3= 4-ciano-fenilo

I47a: 4-[4-Metil-5-(cis-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I47b: 4-[4-Metil-5-(trans-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

El compuesto I47 se preparó mediante el procedimiento descripto en el ejemplo I42 usando los intermedios y reactivos apropiados (protocolo A). El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 20% de acetato de etilo para dar los cis y trans isómeros.
Rendimiento= 68,6%

Compuesto cis: I47a

^{1}H-NMR (400MHz, DMSO) δ ppm: 0,92 (d, 3H), 1,38-1,68 (m, 9H), 2,85-2,92 (m, 1H), 3,55 (s, 3H), 7,80 (dd, 2H), 7,92 (dd, 2H).
MS (m/z) / M+1= 313

Compuesto trans: I47b

^{1}H-NMR (400MHz, DMSO) δ ppm: 0,88 (d, 3H), 0,94-1,09 (m, 2H), 1,30-1,45 (m, 3H), 1,64-1,83 (m, 4H), 2,48-2,60 (m, 1H), 3,52 (s, 3H), 7,80 (dd, 2H), 7,92 (dd, 2H).
MS (m/z) / M+1= 313

Ejemplo I48: R_1= trans-4-hidroxiciclohexilo, R_2= metilo, R_3= 4-ciano-fenilo

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

El compuesto I48 se preparó mediante el procedimiento descripto en el ejemplo I42 usando los intermedios y reactivos apropiados (protocolo A). Usando 0,86 mmol de tiadiazolio, un exceso de clorhidrato de trans-4-aminociclohexanol (7,7 mmol) y 8,6 mmol de trietilamina. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 30% de acetato de etilo.

Rendimiento= 74%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,18-1,42 (m,4H), 1,73-1,89 (m,4H), 2,52-2,62 (m,1H), 3,40-3,50 (m,1H), 3,53 (s, 3H), 4,50 (s, 1H), 7,80 (dd, 2H), 7,92 (dd, 2H).

MS (m/z) / M+1= 315

HPLC (pureza uv, λ= 214 nm)= 99,9%

Ejemplo I49: R_1= exo-2-norbornilo, R_2= metilo, R_3= 4-ciano-fenilo

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

El compuesto I49 se preparó mediante el procedimiento descripto en el ejemplo I48 usando los intermedios y reactivos apropiados (protocolo A). El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 8% de acetato de etilo.

Rendimiento= 64%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,20 (m, 3H), 1,26-1,35 (m, 1H), 1,40-1,53 (m, 2H), 1,56-1,61 (m, 1H), 1,70-1,79 (m, 1H), 2,09-2,14 (m, 1H), 2,24-2,29 (m, 1H), 2,71-2,78 (m, 1H), 3,52 (s, 3H), 7,80 (dd, 2H), 7,91 (dd, 2H).

MS (m/z) / M+1= 311

HPLC (pureza uv, λ= 214 nm)= 99,2%

Ejemplo I50: R_1= (1R*, 2R*)-2-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-ciano-fenilo

4-[5-((1R*, 2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

El compuesto I50 se preparó mediante el procedimiento descripto en el ejemplo I48 usando los intermedios y reactivos apropiados (protocolo A). El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 50% de acetato de etilo.

Rendimiento= 74%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,58-1,75 (m, 3H), 1,80-1,90 (m, 1H), 2,38-2,49 (m, 1H), 3,30-3,40 (m, 1H), 3,55 (s, 3H), 4,50 (s, 1H), 7,80 (dd, 2H), 7,92 (dd, 2H).

MS (m/z) / M+1= 315

HPLC (pureza uv, λ= 214 nm)= 99,9%

Ejemplo I51: R_1= (1R*, 2S*)-2-hidroxiciclohexilo, R_2= metilo, R_3= 4-ciano-fenilo

4-[5-((1R*,2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

El compuesto I51 se preparó mediante el procedimiento descripto en el ejemplo I42 usando los intermedios y reactivos apropiados (protocolo A). Se agregaron perclorato de 1,3,4-tiadiazolio (0,287 mmol, 100 mg) en etanol (6 ml), clorhidrato de cis-2-aminociclohexanol (2,58 mmol, 390 mg) y trietilamina (2,87 mmol, 400 µl). El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 30% de acetato de etilo.

Rendimiento= 72%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,80 (m, 8H), 2,83-2,97 (m, 1H), 3,52-3,70 (m, 4H), 4,10-4,20 (m, 1H), 7,80 (dd, 2H), 7,94 (dd, 2H).

MS (m/z) / M+1= 315

HPLC (pureza uv, λ = 214 nm)= 98,7%

Ejemplos I52-a e I52-b: R_1= 3-hidroxiciclohexilo, R_2= metilo, R_3= 4-ciano-fenilo

I52-a: 4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

I52-b: 4-[5-((1R*, 3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

Los compuestos I52-a e I52-b se prepararon mediante el procedimiento descripto en el ejemplo I42 usando los intermedios y reactivos apropiados (protocolo A). Una mezcla de perclorato de 1,3,4-tiadiazolio (3c) (3,5 mmol, 1,22 g) en etanol (80 ml), 3-aminociclohexanol racémico (4,2 mmol, 485 mg) y trietilamina (4,2 mmol, 587 µl) se agitó a reflujo durante 4 h. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 60% de acetato de etilo para dar 120 mg del trans isómero y 260 mg del cis isómero.

1R*, 3R* isómero (I52a)

Rendimiento= 11%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,35-1,50 (m, 2H), 1,50-1,70 (m, 6H), 3,04-3,12 (m, 1H), 3,54 (s, 3H), 3,88-3,96 (m, 1H), 4,44 (d, 1H), 7,80 (dd, 2H), 7,94 (dd, 2H).

1R*, 3S* isómero (I52b)

^{1}H (400MHz, DMSO) δ ppm: 1,03-1,30 (m, 4H), 1,64-1,78 (m, 2H), 1,78-1,87 (m, 1H), 1,98-2,04 (m, 1H), 2,58-2,70 (m, 1H), 3,40-3,58 (m, 4H), 4,61 (s, 1H), 7,44 (s, 1H), 7,70 (dd, 2H), 7,95 (dd, 2H), 8,07 (s, 1H).

Ejemplo I53: R_1= (1R*, 3R*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-(metilsulfonil)fenilo

(1R*, 3R*))-3-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol

El compuesto I53 se preparó mediante el procedimiento descripto en el ejemplo I42 usando los intermedios y reactivos apropiados (protocolo A). Una mezcla de perclorato de 1,3,4-tiadiazolio (3b) (1 mmol, 400 mg), etanol (25 ml), 3-aminociclohexanol racémico (1,2 mmol, 140 mg) y trietilamina (2,5 mmol, 350 µl) se agitó a reflujo durante 3 h. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 50% de acetato de etilo. El producto luego se purificó

mediante HPLC sobre una columna de C_{18} de Kromasil con un gradiente de acetonitrilo/agua de 95/5 a 5/95 para dar el producto puro.

Rendimiento= 10%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,30-1,69 (m, 8H), 3,00-3,10 (m, 1H), 3,21 (s, 3H), 3,52 (s, 3H), 3,82-3,95 (m, 1H), 4,35 (d, 1H), 7,85 (dd, 2H), 7,98 (dd, 2H)

MS (m/z) / M+1= 367/369

HPLC (pureza uv, λ= 214 nm)= 98,9%

Ejemplo I54: R_1= (1R*, 3R*)-3-Hidroxi-ciclohexilo, R_2= metilo, R_3= ácido 4-benzoico

Ácido 4-[5-(1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico

A una solución de I52a (3,18 mmol, 1 g) en isopropanol (20 ml), se agregó una solución de KOH [6N] (15,9 mmol, 2,6 ml) y la mezcla se agitó a reflujo durante 4 días. La mezcla se acidificó a pH= 6-7 con una solución de HCl y se concentró bajo presión reducida para dar el derivado del ácido carboxílico I54.

^{1}H (400MHz, DMSO) δ ppm : 1,32-1,70 (m, 8H), 3,03-3,12 (m, 1H), 3,50 (s, 3H), 3,85-3,95 (m, 1H), 4,35-4,50 (m, 1H), 7,75 (dd, 2H), 8,00 (dd, 2H), 13,15 (s, 1H)

Ejemplo I55: R_1= (1R*, 3R*)-3-hidroxiciclohexilo, R_2= metilo, R_3= 4-[N-(2-morfolin-4-il-etil)]benzamida

4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-morfolin-4-il-etil)-benzamida

El compuesto I55 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I54 como material inicial.

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 4% de metanol para dar el producto deseado.

Rendimiento= 14%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1,35-1,70 (m, 8H), 2,35-2,52 (m, 6H), 3,02-3,12 (m, 1H), 3,32-3,45 (m, 2H), 3,50-3,62 (m, 7H), 3,88-3,95 (m, 1H), 4,40 (d, 1H) 7,72 (dd, 2H), 7,92 (dd, 2H), 8,50 (s, 1H).

MS (m/z) / M+1= 446

HPLC (pureza uv, λ= 214 nm)= 96,6%

Ejemplo I56: R_1= trans-4-hidroxiciclohexilo, R_2= metilo, R_3= ácido 4-benzoico

Ácido 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico

A una solución de I48 (1,9 mmol, 600 mg) en etanol (15 ml) e isopropanol (15 ml), se agregó una solución de KOH [6N] (5,7 mmol, 960 µl) y se agitó a reflujo durante 7 h. La mezcla se acidificó a pH= 6-7 con una solución de HCl y luego se concentró bajo presión reducida para dar el derivado del ácido carboxílico I56.

^{1}H-RMN (400MHz, DMSO) δ ppm: 1,22-1,32 (m, 2H), 1,60-1,80 (b, 2H), 1,90-2,04 (m, 4H), 3,41-3,50 (m, 1H), 4,00 (s, 3H), 7,80-7,90 (m, 2H), 8,00-8,10 (m, 2H), 11,00 (s, 1H).

Ejemplo I57: R_1= trans-4-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-(N-2-hidroxi-1,1-dimetil-etil)benzamida

4-[5-(trans-4-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida

El compuesto I57 se preparó mediante el procedimiento descripto en el ejemplo I37.11 usando I56 como material inicial. El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 9% de metanol para dar el producto esperado.

Rendimiento= 20%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1,15-1,45 (m, 10H), 1,70-1,90 (m, 4H), 2,50-2,60 (m, 1H), 3,40-3,55 (m, 6H), 4,50 (d, 1H) 4,85 (d, 1H), 7,60 (s, 1H), 7,70 (dd, 2H), 7,89 (dd, 2H).

MS (m/z) / M+1= 405

HPLC (pureza uv, λ= 214 nm)= 99,9%

Ejemplo I58: R_1= (1R*, 3R*)-3-hidroxi-ciclohexilo, R_2= methyl, R_3= 4-(N-2-hidroxi-1,1-dimetil-etil)benzamida

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]thiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida

El compuesto I58 se preparó mediante el procedimiento descripto en el ejemplo I55 usando los intermedios y reactivos apropiados (I54 y 1,1-dimetil-2-etanolamina).

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 5% de metanol para dar el producto deseado.

Rendimiento= 58%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1,20-1,70 (m, 14H), 3,02-3,12 (m, 1H), 3,40-3,60 (m, 5H), 3,85-3,95 (m, 1H), 4,40 (d, 1H), 4,85 (d, 1H), 7,60 (s, 1H), 7,68 (dd, 2H), 7,85 (dd, 2H)

MS (m/z) / M+1= 405

HPLC (pureza uv, λ= 214 nm)= 94,4%

Ejemplo I59: (1R*, 3R*)-3-hidroxiciclohexilo, R_2= metilo, R_3= 4-(N-terc-butil)-benzamida

N-terc-Butil-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

El compuesto I59 se preparó mediante el procedimiento descripto en el ejemplo I55 usando los intermedios y reactivos apropiados (I54 e isobutilamina). El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 10%.

Rendimiento= 33%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1,30-1,70 (m, 17H), 3,02-3,12 (m, 1H), 3,50 (s, 3H), 3,85-3,95 (m, 1H), 4,40 (d, 1H), 7,68 (dd, 2H), 7,80-7,90 (m, 3H).

MS (m/z) / M+1= 389

HPLC (pureza uv, λ= 214 nm)= 94,1%

Ejemplo I60: R_1= (1R*, 3R*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-[N-(1,1-dimetil-3-oxo-butil)]-benzamida

N-(1,1-dimetil-3-oxo-butil)-4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

A una suspensión de hidrogenoxalato de diacetona (3 mmol, 616 mg) en DMF (6 ml) bajo una atmósfera de nitrógeno, se agregó resina de morfolina [3,47 mmol/g] (7 mmol, 2 g), y la mezcla se agitó a temperatura ambiente durante 30 minutos y luego se filtró. Una mezcla del ácido I54 (0,6 mmol), el filtrado, N,N-diisopropiletilamina (1,32 mmol, 227 µl), hexafluorofosfato de benzotriazol-1-iloxitris(dimetilamino) fosfonio (0,72 mmol, 318 mg), 1-hidroxi-7-azabenzotriazol (0,3 mmol, 82 mg) se agitó a temperatura ambiente durante 4 h. La mezcla se concentró y luego se diluyó en diclorometano. La capa orgánica se lavó con una solución saturada de cloruro de amonio, una solución saturada de $NaHCO_3$, con agua, solución salina, se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 8% de metanol. El compuesto se purificó mediante HPLC (columna de Kromasil de C_{18}) eluyendo con acetonitrilo/agua de 95/5 a 5/95 para dar el producto deseado.

Rendimiento: 10%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1,30-1,70 (m, 14H), 2,05 (s, 3H), 2,92-3,10 (m, 3H), 3,50 (s, 3H), 3,85-3,95 (m, 1H), 4,40 (d, 1H), 7,68 (dd, 2H), 7,85 (dd, 2H), 7,95 (s, 1H).

MS (m/z) / M+1= 431

HPLC (pureza uv, λ= 214 nm)= 99,3%

Ejemplo I61: R_1= (1R*,3R*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-[N-(2-ciano-1,2,2-trimetil-etil)]-benzamida

N-(2-Ciano-1,2,2-trimetil-etil)-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

El compuesto I61 se preparó mediante el procedimiento descripto en el ejemplo I55 usando los intermedios y reactivos apropiados (I54 y 2-amino-2,3-dimetilbutanonitrilo).
El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 70% de acetato de etilo para dar el producto del título.
Rendimiento= 8%

^{1}H-NMR (400MHz, DMSO): δ ppm: 0,95 (d, 3H), 1,10 (d, 3H), 1,30-1,70 (m, 11H), 2,45-2,65 (m, 1H), 3,00-3,10 (m, 1H), 3,50 (s, 3H), 3,85-3,95 (m, 1H), 4,40 (d, 1H), 7,70 (dd, 2H), 7,90 (d, 2H), 8,65 (s, 1H).

MS (m/z) / M+1= 428

HPLC (pureza uv, λ= 214 nm)= 99,4%

Ejemplo I62: R_1= (1R*, 3R*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-(N-1-metoxicarbonil-ciclopropil)-benzamida

Metil éster del ácido 1-{4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoilamino}-ciclopropanocarboxílico

El compuesto I62 se preparó mediante el procedimiento descripto en el ejemplo I37.24 usando los intermedios y reactivos apropiados (I55 y clorhidrato de metil éster del ácido 1-aminociclopropano-1-carboxílico).

El residuo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de diclorometano que contenía del 0% al 12% de metanol y mediante HPLC (Columna de Hypersil) con un gradiente de acetonitrilo/agua de 95/5 a 5/95 para dar el producto deseado.

Rendimiento= 32%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1,12-1,20 (m, 2H), 1,33-1,50 (m, 4H), 1,50-1,70 (m, 6H), 3,03-3,12 (m, 1H), 3,52 (s, 3H), 3,60 (s, 1H), 3,89-3,98 (m, 1H), 4,40 (d, 1H), 7,72 (dd, 2H), 7,94 (d, 2H), 9,17 (s, 1H).

MS (m/z) / M+1= 431

HPLC (pureza uv, λ= 214 nm)= 97,9%

Ejemplo I63: R_1= ciclopentilo, R_2= metilo, R_3= 4-benzamida

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

A una solución del compuesto I42 (0,53 mmol, 150 mg) en etanol (17 ml), se agregó una solución de Na_2CO_3 [3N] (5,6 mmol, 1,88 ml) y una solución de H_2O_2 al 30% en agua (1,54 ml). La solución se agitó toda la noche a temperatura ambiente. A la mezcla, se agregó una solución de H_2O_2 al 30% en agua (770 µl) y la solución se dejó agitar a temperatura ambiente durante dos días (hasta que se completó la reacción). La mezcla resultante se concentró mediante la destilación del solvente y el material crudo se precipitó en agua. El precipitado se filtró, se lavó varias veces con agua y se secó para dar el producto puro.

Rendimiento= 53,4%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,43-1,95 (m, 8H), 3,18-3,28 (m, 1H), 3,52 (s, 3H), 7,44 (s, 1H), 7,70 (dd, 2H), 7,95 (dd,2H), 8,05 (s, 1H).

MS (m/z) / M+1= 303

HPLC (pureza uv, λ= 214 nm)= 98,04%

Ejemplo I64: R_1= cicloheptilo, R_2= metilo, R_3= 4-benzamida

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

El compuesto I64 se preparó mediante el procedimiento descripto en el ejemplo I63 usando los intermedios (I63) y reactivos apropiados.

El precpitado se filtró, se lavó varias veces con agua y se secó para dar el producto puro.

Rendimiento= 59,88%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,40-1,83 (m, 12H), 2,78-2,85 (m, 1H), 3,52 (s, 3H), 7,44 (s, 1H), 7,72 (dd, 2H), 7,97 (dd,2H), 8,07 (s, 1H).

MS (m/z) / M+1= 331

HPLC (pureza uv, λ= 214 nm)= 98,98%

Ejemplo I65: R_1= 4-fluoro-fenilo, R_2= metilo, R_3= 4-benzamida

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

El compuesto I65 se preparó mediante el procedimiento descripto en el ejemplo I63 usando los intermedios I44 y reactivos apropiados.

El precpitado se filtró, se lavó varias veces con agua y se secó para dar el producto puro.

Rendimiento= 72,43%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,72 (s, 3H), 7,02-7,40(m, 2H), 7,15-7,24 (m, 2H), 7,44 (s, 1H), 7,72 (dd, 2H), 7,95 (dd,2H), 8,05 (s, 1H).

MS (m/z) / M+1= 329

HPLC (pureza uv, λ= 214 nm)= 97,7%

Ejemplo I66: R_1= 3-hidroxi-fenilo, R_2= metilo, R_3= 4-benzamida

4-[5-(3-Hdroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

El compuesto I66 se preparó mediante el procedimiento descripto en el ejemplo I63 usando los intermedios (I45) y reactivos apropiados.

El precpitado se filtró, se lavó varias veces con agua y se secó para dar el producto puro.

Rendimiento= 59,84%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,70 (s, 3H), 6,44-6,52 (m, 3H), 7,18 (t, 1H), 7,44 (s, 1H), 7,75 (dd, 2H), 7,97 (dd, 2H), 8,06 (s, 1H), 9,40 (s, 1H).

MS (m/z) / M+1= 327

HPLC (pureza uv, λ= 214 nm)= 99,68%

Ejemplo I67: R_1= ácido 4-fluoro-3-benzoico, R_2= metilo, R_3= 4-benzamida

Ácido 5-[5-(4-Carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico

El compuesto I67 se preparó mediante el procedimiento descripto en el ejemplo I63 usando los intermedios (I46) y reactivos apropiados.

El precpitado se filtró, se lavó varias veces con agua y se secó para dar el producto puro.

Rendimiento= 44,41%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,72 (s, 3H), 7,25-7,32 (m, 2H), 7,43-7,50 (m, 2H), 7,78 (dd, 2H), 7,95 (dd, 2H), 8,05 (s, 1H), 13,30 (b, 1H).

MS (m/z) / M+1= 373

HPLC (pureza uv, λ = 214 nm)= 90,52%

Ejemplo I68: R_1= trans-4-metil-ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-[4-Metil-5-(trans-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

El compuesto I68 se preparó mediante el procedimiento descripto en el ejemplo I63 usando los intermedios (I47b) y reactivos apropiados.

El precpitado se filtró, se lavó varias veces con agua y se secó para dar el producto puro.

Rendimiento= 52,53%

^{1}H-NMR (400MHz, DMSO) δ ppm: 0,90 (d, 3H), 0,95-1,08 (m, 2H), 1,30-1,45 (m, 3H), 1,67-1,85 (m, 4H), 2,50-2,60 (m, 1H), 3,52 (s, 3H), 7,44 (s, 1H), 7,72 (dd, 2H), 7,95 (dd, 2H), 8,05 (s, 1H).

MS (m/z) / M+1= 331

HPLC (pureza uv, λ= 214 nm)= 99,7%

Ejemplo I69: R_1= trans-4-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

A una suspensión de I48 (0,477 mmol, 150 mg) en etanol (17 ml), se agregó una solución de Na_2CO_3 [3N] (5,1 mmol, 1,7 ml) y una solución de H_2O_2 al 30% en agua (1,4 ml) y la mezcla se agitó toda la noche a temperatura ambiente. Esta mezcla se vertió en agua antes de la extracción con acetato de etilo. La capa orgánica se lavó con agua y con una solución saturada de NaCl, se secó sobre sulfato de magnesio, se filtró y se destiló para dar un residuo que se purificó mediante cromatografía sobre gel de sílice (eluido con un gradiente de

diclorometano/metanol de 100/0 a 98/2) para dar el producto puro.

Rendimiento= 31%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,42 (m, 4H), 1,75-1,90 (m, 4H), 2,50-2,63 (m, 1H), 3,40-3,52 (m,1H), 3,50 (s, 3H), 4,55 (s,1H), 7,44 (s, 1H), 7,72 (dd, 2H), 7,98 (dd, 2H), 8,07 (s, 1H).

MS (m/z) / M+1= 332/333

HPLC (pureza uv, λ= 214 nm)= 97,3%

Ejemplo I70: R_1= biciclo[2.2.1]hept-2-ilo, R_2= metilo, R_3= 4-benzamida

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

El compuesto I70 se preparó mediante el procedimiento descripto en el ejemplo I69 usando los intermedios (I49) y reactivos apropiados.

El residuo se purificó mediante cromatografía sobre gel de sílice (eluido con un gradiente de diclorometano/metanol de 100/0 a 90/10) para dar el producto deseado.

Rendimiento= 66%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,25 (m,3H), 1,28-1,40 (m,1H), 1,40-1,67 (m,4H), 2,10-2,18 (m,1H), 2,25-2,32 (m,1H),

2,70-2,80 (m,1H), 3,52 (s, 3H), 7,50 (s, 1H), 7,72 (dd, 2H), 7,97 (dd, 2H), 8,10 (s, 1H).

MS (m/z) / M+1= 329

HPLC (pureza uv, λ= 214 nm)= 99,9%

Ejemplo I71: R_1= (1R*,2R*)-2-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-[5-((1R*,2R*)-2-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

El compuesto I71 se preparó mediante el procedimiento descripto en el ejemplo I69 usando los intermedios (I50) y reactivos apropiados.

El residuo se purificó mediante cromatografía sobre gel de sílice (eluido con un gradiente de diclorometano/metanol de 100/0 a 90/10) para dar el producto deseado.

Rendimiento= 44%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,39 (m, 4H), 1,60-1,75 (m, 3H), 1,80-1,90 (m,1H), 2,35-2,45 (m, 1H), 3,50 (s, 3H), 4,55 (s,1H), 7,50 (s, 1H), 7,72 (dd, 2H), 7,96 (dd, 2H), 8,05 (s, 1H).

MS (m/z) / M+1=333

HPLC (pureza uv, λ= 214 nm)= 97,4%

Ejemplo I72: R_1= (1R*,2S*)-2-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-[5-((1R*,2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

A una suspensión de I51 (0,16 mmol, 50 mg) en DMSO (100 µl), se agregó K_2CO_3 (0,022 mmol, 3 mg), una solución de H_2O_2 al 30% en agua (20 µl) y la mezcla se agitó toda la noche a temperatura ambiente. A esta mezcla se le agregó agua y se dejó agitar la solución durante 15 minutos. El precipitado se filtró y se secó bajo presión reducida para dar el producto deseado.

Rendimiento= 68%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,25-1,38 (m, 2H), 1,40-1,80 (m, 6H), 2,85-2,90 (m, 1H), 3,57 (s, 3H), 3,60-3,68 (m, 1H), 4,10 (d,1H), 7,40 (s, 1H), 7,70 (dd, 2H), 7,95 (dd, 2H), 8,05 (s, 1H).

MS (m/z) / M+1= 333

HPLC (pureza uv, λ= 214 nm)= 98,8%

Ejemplo I73: R_1= (1R*,3R*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

El compuesto I73 se preparó mediante el procedimiento descripto en el ejemplo I69 usando los intermedios (I52-a) y reactivos apropiados.

El residuo se concentró bajo presión reducida y se agitó en agua varias horas, se filtró y se secó bajo vacío para dar el producto deseado.

Rendimiento= 70%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,30-1,70 (m, 8H), 3,10 (s, 1H), 3,52 (s, 3H), 3,93 (s,1H), 4,42 (d, 1H), 7,43 (s, 1H), 7,70 (dd, 2H), 7,96 (dd,2H), 8,05 (s, 1H).

MS (m/z) / M+1=333

HPLC (pureza uv, λ= 214 nm)= 98,3%

Ejemplo I74: R_1= (1R*,3S*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-yl]-benzamida

El compuesto I74 se preparó mediante el procedimiento descripto en el ejemplo I69 usando los intermedios (I52-b) y reactivos apropiados.

El residuo se concentró bajo presión reducida y se agitó en agua varias horas, se filtró y se secó bajo vacío para dar el producto deseado.

Rendimiento= 83%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,05-1,30 (m, 4H), 1,65-1,78 (m, 2H), 1,78-1,88 (m, 1H), 1,95-2,05 (m, 1H), 3,40-3,58 (m, 4H), 4,60 (s, 1H), 7,45 (s, 1H), 7,70 (dd, 2H), 7,95 (dd, 2H), 8,05 (s, 1H).

MS (m/z) / M+1=333

HPLC (pureza uv, λ= 214 nm)= 99,4%

Ejemplo I74.1: R_1= 3-oxo-ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-[4-Metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

A una solución de I74 (0,15 mmol, 50 mg) en diclorometano (0,5 ml), se agregó perrutenato de tetrapropilamonio (0,5% en moles, 3 mg), N-óxido de 4-metilmorfolina (0,22 mmol, 28 mg) y un tamiz molecular (500 mg/mol, 75 mg) y la mezcla se agitó a temperatura ambiente toda la noche. La mezcla se filtró a través de un tampón de gel de sílice (eluido con diclorometano/metanol de 100/0 a 95/5), el filtrado se concentró bajo presión reducida y se lavó con dietiléter para dar el producto puro.

Rendimiento= 18%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,63-1,82 (m, 2H), 1,89-2,10 (m, 2H), 2,21-2,50 (m, 4H), 3,15-3,30 (m, 1H), 3,52 (s, 3H), 7,45 (s, 1H), 7,70 (dd, 2H), 7,98 (dd, 2H), 8,08 (s, 1H).

MS (m/z) / M+1=331

HPLC (pureza uv, λ= 214 nm)= 98,7%

Ejemplo I75: R_1= 3,3-difluoro-ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-[5-(3,3-Difluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

A una solución de I52-b (0,318 mmol, 100 mg) en diclorometano (1 ml), se agregó perrutenato de tetrapropilamonio (0,5% en moles, 6 mg), N-óxido de 4-metilmorfolina (0,477 mmol, 56 mg) y un tamiz molecular (500 mg/mol, 160 mg). La mezcla se agitó a temperatura ambiente durante 3 h, se filtró a través de gel de sílice (eluido con ciclohexano/acetato de etilo de 100/0 a 60/40) y se concentró bajo presión reducida para dar 4-[4-metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo

Rendimiento= 90%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,60-1,80 (m, 2H), 1,87-2,10 (m, 2H), 2,21-2,30 (m, 3H), 2,55-2,60 (m, 1H), 3,15 (s, 1H), 3,52 (s, 3H), 7,82 (dd, 2H), 7,92 (dd, 2H).

A una solución de esta cetona (0,288 mmol, 90 mg) en diclorometano (0,5 ml) se agregó una solución de desoxo-flúor (0,49 mmol, 90 µl) en diclorometano (1 ml) y etanol (0,346 mmol, 5 µl) y la mezcla se agitó toda la noche a temperatura ambiente. La mezcla se vertió en una solución saturada de $NaHCO_3$ (pH=7) y la capa acuosa se extrajo con diclorometano. La capa orgánica se lavó con agua y solución salina, se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida para dar un residuo que se purificó por cromatografía sobre gel de sílice (eluido con un gradiente de ciclohexano/acetato de etilo de 100/0 a 80/20) para dar el compuesto di-fluoro puro: 4-[5-(3,3-dfluoro-cilohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo.

Rendimiento = 12%

^{1}H-RMN (400MHz, DMSO) δ ppm: 1,40-1,55 (m, 2H), 1,78-1,90 (m, 4H), 1,95-2,09 (m, 1H), 2,15-2,28 (m, 1H), 2,80-2,90 (m, 1H), 3,55 (s, 3H), 7,82 (dd, 2H), 7,92 (dd, 2H).

A una solución de este derivado de difluoro (0,036 mmol, 12 mg) en etanol (1,6 ml) se agregó una solución de Na_2CO_3 [3N] (0,6 mmol, 200 µl) y una solución de H_2O_2 al 30% en agua (50 µl) y la mezcla se agitó a 40°C toda la noche. Luego, se agregó una solución de H_2O_2 al 30% en agua (130 µl) y la solución se

dejó agitar durante 12 h a 40°C. La mezcla se concentró bajo presión reducida. El residuo se agitó en agua varias horas, se filtró, se lavó con éter y se secó bajo vacío para dar el compuesto deseado.

Rendimiento= 40%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,33-1,53 (m, 2H), 1,70-1,90 (m, 4H), 1,90-2,05 (m, 1H), 2,15-2,28 (m, 1H), 2,80-2,90 (m, 1H), 3,55 (s, 3H), 7,48 (s, 1H), 7,72 (dd, 2H), 7,96 (dd, 2H), 8,08 (s, 1H)

MS (m/z) / M+1=353

HPLC (pureza uv, λ = 214 nm)= 98,7%

Ejemplo I76: R_1= (1R*,3R*)-3-fluoro-ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-[5-((1R*,3R*)-3-Fluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

A una solución de I52-b (1,59 mmol, 500 mg) en diclorometano (4 ml), se agregó 4-morfolinazufretrifluoruro (3,18 mmol, 390 µg) a -15°C gota a gota bajo una atmósfera de nitrógeno. La mezcla se calentó a temperatura ambiente durante 30 minutos y se vertió en una solución saturada de $NaHCO_3$ (pH=7). La fase

acuosa se extrajo con diclorometano. La fase orgánica se lavó con agua y solución salina, se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida para dar un residuo que se purificó por cromatografía sobre gel de sílice (eluido con un gradiente de ciclohexano/acetato de etilo de 100/0 a 70/30) para dar 4-[5-(ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo y un intermedio mono-fluoro, (4-[5-((trans)-3-fluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo):

Rendimiento= 14%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,40-1,50 (m, 1H), 1,58-1,85 (m, 6H), 1,92-2,05 (m, 1H), 2,95-3,05 (m, 1H), 3,55 (s, 3H), 4,95 (d, 1H), 7,83 (dd, 2H), 7,95 (dd, 2H).

A una solución de este intermedio fluoro (0,2 mmol, 65 mg) en etanol (8,.7 ml) se agregó una solución de Na_2CO_3 [3N] (2,61 mmol, 870 µl) y una solución de H_2O_2 al 30% en agua (705 µl) y la mezcla se agitó a 40°C toda la noche. Se agregó una solución de H_2O_2 al 30% en agua (705 µl) y la solución se dejó agitar durante 10 h a 40°C. La mezcla se concentró bajo presión reducida. El residuo se agitó en agua varias horas, se filtró, se lavó con éter y se secó bajo vacío para dar el compuesto del título I76.

Rendimiento= 58%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,35-1,52 (m, 1H), 1,52-1,90 (m, 6H), 1,90-2,08 (m, 1H), 2,93-3,08 (m, 1H), 3,55 (s, 3H), 5,00 (d, 1H), 7,50 (s, 1H), 7,78 (dd, 2H), 7,99 (dd, 2H), 8,10 (s, 1H).

MS (m/z) / M+1= 335

HPLC (pureza uv, λ= 214 nm)= 96,6%

Ejemplo I77: R_1= 3-ciclohexeno, R_2= metilo, R_3= 4-benzamida

4-[5-(Ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida

A una solución de 4-[5-(ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo del protocolo I76 (0,94 mmol, 280 mg) en etanol (41 ml), se agregó una solución de Na_2CO_3 [3N] (12,3 mmol, 4,1 ml), y una solución de H_2O_2 al 30% en agua (3,33 ml). La mezcla se agitó toda la noche a temperatura ambiente y se concentró bajo presión reducida. El residuo se agitó en agua varias horas, se filtró y se secó bajo vacío para dar el producto puro.

Rendimiento= 64%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,48-1,65 (m, 1H), 1,72-2,35 (m, 5H), 2,82-2,92 (m, 1H), 3,55 (s, 3H), 5,65 (t, 2H), 7,50 (s, 1H), 7,71 (dd, 2H), 7,95 (dd, 2H), 8,09 (s, 1H)

MS (m/z) / M+1= 315

HPLC (pureza uv, λ= 214 nm)= 96,1%

Ejemplo I78: R_1= (1R*,3R*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-(1H-tetrazol-5-il)-fenilo

(1R*,3R*)-3-{3-Metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-ilidenamino}-ciclohexanol

A una solución de I52-a (1,27 mmol, 400 mg) en tolueno (3 ml), se agregaron azida de sodio (1,65 mmol, 108 mg) y clorhidrato de trietilamina (1,65 mmol, 228 mg) y la mezcla se calentó a reflujo durante 24 horas. La mezcla de la reacción mixture se enfrió a temperatura ambiente, se acidificó con una solución de HCl [0,1N], y luego se basificó a pH=6-7 con una solución saturada de $NaHCO_3$. La fase acuosa se extrajo con diclorometano y la capa orgánica se lavó con una solución saturada de NaCl, se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida. El residuo se cromatografió sobre una columna de gel de sílice usando un gradiente de diclorometano que contenía del 0% al 20% de metanol para dar el compuesto del título.

Rendimiento: 50%

^{1}H-NMR (400MHz, DMSO): δ ppm: 1,30-1,70 (m, 8H), 3,00-3,15 (m, 1H), 3,50 (s, 3H), 3,85-3,98 (m, 1H), 4,40 (s, 1H), 7,75 (dd, 2H), 8,10 (d, 2H).

MS (m/z) / M+1= 358

HPLC (pureza uv, λ= 214 nm)= 99,9%

Ejemplo I79: R_1= ácido 3-(6-hidroxi)-benzoico, R_2= metilo, R_3= 4-cloro-fenilo

Ácido 3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico

El compuesto del título se preparó mediante el procedimiento del ejemplo I3 usando etanol como solvente e intermedios y reactivos apropiados. El residuo se cromatografió dos veces sobre gel de sílice eluyendo con diclorometano que contenía del 0% al 7% de metanol. El producto aislado se lavó con agua para dar el producto deseado.

Rendimiento= 9,7%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,62 (s, 3H), 6,80 (t, 1H), 7,12 (d, 1H), 7,40-7,46 (m, 3H), 7,59 (d, 2H).

MS (m/z) / M+1 =362/364.

HPLC (pureza uv, λ= 214 nm): 98,36%

Ejemplo I80: R_1= ácido 3-benzoico, R_2= metilo, R_3= 4-ciano-fenilo

Ácido 3-[5-(4-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

Una suspensión de perclorato de 1,3,4-tiadiazolio (3c) (4,873 mmol, 1,70 g), ácido 3-benzoico (4,87 mmol, 0,668 g) y trietilamina (4,873 mmol, 0,679 ml) en etanol (20 ml) se refluyó durante 3,5 h. Después de enfriar, el sólido formado se filtró y se lavó con EtOH frío y éter. El sólido se secó bajo presión reducida para dar 1,25 g del compuesto esperado.

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,87 (s, 3H), 7,39-7,42 (m, 1H), 7,60-7,65 (m, 1H), 7,70 (s, 1H), 7,78-7,82 (m, 1H), 7,96-8,00 (d, 2H), 8,00-8,04 (d, 2H).

MS (m/z) / M+1 = 337/338

HPLC (pureza uv, λ= 214 nm)= 93,22%

Ejemplo I80.1: R_1= ácido 3-benzoico, R_2= metilo, R_3= 4-benzamida

Ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

Ácido sulfúrico concentrado (19,8 mmol, 1,06 ml) y agua (0,13 ml) se agregaron respectivamente, a 0°C, a I80 (0,595 mmol, 0,200 g) y la mezcla de la reacción se calentó a 80°C durante 1h30. Luego, se agregó hielo a la mezcla y el precipitado formado se filtró y se purificó mediante cromatografía sobre gel de sílice, eluyendo con una mezcla de ácido

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acético/diclorometano/metanol (1,5/85/13,5). El producto aislado se trituró en metanol y el sólido se filtró y se secó bajo vacío para dar el producto del título.

Rendimiento= 34%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,76 (s, 3H), 7,30 (d, 1H), 7,46-7,55 (m, 2H), 7,62 (s, 1H), 7,67 (d, 1H), 7,80 (d, 2H), 7,99 (d, 2H), 8,09 (s, 1H), 12,90-13,02 (d, 1H).

MS (m/z) / M+1= 355/356

HPLC (pureza uv, λ= 214 nm): 96,37%

Ejemplo I81: R_1= ácido 4-fluoro-3-benzoico, R_2= metilo, R_3= 4-(metilsulfonil)-fenilo

Ácido 2-fluoro-5-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I81 se preparó mediante el procedimiento descripto en el ejemplo I4 (protocolo A) con los reactivos apropiados y usando 1,0 eq de trietilamina. La mezcla de la reacción se concentró y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con diclorometano y luego una mezcla de diclorometano/MeOH/AcOH (98/1,8/0,2).

Rendimiento= 13%

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,19 (s, 3H), 3,57 (s, 3H), 7,11-7,19 (m, 2H), 7,31-7,34 (m, 1H), 3,50, 7,79 (d, 2H), 7,85 (d, 2H), 13,08-13,14 (b, 1H).

MS (m/z) / M+1 = 408/409

HPLC (pureza uv, λ= 214 nm)= 98,3%

Ejemplo I82: R_1= ciclohexilo de ácido 3-carboxílico, R_2= metilo, R_3= 4-(metilsulfonil)-fenilo

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico

I82 se preparó mediante el procedimiento descripto en el ejemplo I4 con los reactivos apropiados y usando 1,0 eq de trietilamina. La mezcla se filtró y el filtrado se evaporó hasta secarse. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con $CHCl_3$/MeOH (93/7) para dar 15 mg del producto deseado.

Rendimiento= 1,52%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,02-1,24 (m, 4H), 1,58-1,70 (m, 3H), 1,80-1,86 (m, 1H), 2,12-2,19 (m, 1H), 2,44-2,52 (m, 1H), 3,06 (s, 3H), 3,36 (s, 3H), 7,70 (d, 2H), 7,82 (d, 2H), 11,82-11,90 (b, 1H).

MS (m/z) / M+1 = 395/396

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HPLC (pureza uv, λ= 214 nm): 98,76%

Ejemplo I83: R_1= piperidin-1-ilo, R_2= metilo, R_3= 4-(metilsulfonil)-fenilo

[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-piperidin-1-il amina

A una suspensión de perclorato de 1,3,4-tiadiazolio (3b) (1,26 mmol, 0,5 g) en etanol (6 ml) se agregaron 1-aminopiperidina (2,5 mmol, 0,3 ml) luego trietilamina (2,5 mmol, 0,4 ml) y la mezcla se mantuvo a 70°C durante 3 horas. La mezcla se concentró bajo presión reducida. El residuo se recogió en diclorometano, se lavó dos veces con agua, se concentró bajo presión reducida y se purificó por cromatografía sobre gel de sílice (99:1 DCM/MeOH) para dar 0,2 g del compuesto del título.

Rendimiento= 45%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,46 (s, 2H), 1,68-1,71 (m, 4H), 2,77 (s, 4H), 3,07 (s, 3H), 3,65 (s, 3H), 7,81-7,83 (dd, 2H), 7,95-7,97 (dd, 2H).

MS (m/z) / M+1= 353,46

HPLC (pureza uv, λ= 214 nm)= 97,4%

Ejemplo I84: R_1= tetrahidro-piran-4-ilo, R_2= metilo, R_3= 4-(metilsulfonil)-fenilo

[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(tetrahidro-piran-4-il)-amina

A una suspensión de perclorato de 1,3,4-tiadiazolio (3b) (0,7 mmol, 0,3 g) en etanol (4 ml) se agregaron 4-aminotetrahidropirano (1,4 mmol, 0,3 g) y trietilamina (3 mmol, 0,4 ml). La mezcla se mantuvo a 70°C durante 3 horas, se concentró bajo presión reducida. El residuo se recogió en diclorometano, se lavó una vez con agua, se concentró bajo presión reducida y se purificó por cromatografía sobre gel de sílice (99:1 DCM/MeOH) y se lavó con acetato de etilo y heptano para dar 23 mg del compuesto esperado.

Rendimiento= 30%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,68-1,85 (m, 4H), 2,88-2,95 (m, 1H), 3,07 (s, 3H), 3,47-3,57 (m, 2H), 3,65 (s, 3H), 4,01-4,06 (m, 2H), 7,81 (d, 2H), 7,97(d, 2H).

MS (m/z) / M+1= 354,03

HPLC (pureza uv, λ= 214 nm)= 100%.

Ejemplo I85: R_1= ácido 3-benzoico, R_2= metilo, R_3= 4-acetilamino-fenilo

Ácido 3-[5-(4-acetilamino-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

Una suspensión de perclorato de 1,3,4-tiadiazolio (3d) (0,7 mmol, 0,3 g), trietilamina (2,1 mmol, 0,3 ml) y ácido 3-acetamidobenzoico (0,6 mmol, 0,077 g) en etanol (20 ml) se refluyó toda la noche. La mezcla se concentró bajo presión reducida, se purificó por cromatografía sobre gel de sílice (95:5 DCM/MeOH) y se lavó con MeOH para dar 0,01 g del sólido blanco.

Rendimiento= 5%

^{1}H-NMR (400MHz, DMSO) δ ppm: 2,06 (s, 3H), 2,71 (s, 3H), 7,26 (d, 1H), 7,47 (t, 1H), 7,60-7,70 (m, 6H), 10,18 (s, 1H).

MS (m/z) / M+1= 368,95

HPLC (pureza, λ= 214 nm)= 98%

Ejemplo I86: R_1= trans-4-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-acetlamino-fenilo

N-{4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida

Una mezcla de trans-4-aminociclohexanol (0,28 mmol, 0,04 g), trietilamina (0,39 mmol, 0,06 ml) y 3-metil-2-metiltio[1,3,4]tiadiazolio (3d) (0,14 mmol, 0,04 g) se

refluyeron en etanol (1 ml) toda la noche. La mezcla se concentró bajo presión reducida. El residuo se recogió en diclorometano, se lavó una vez con agua, se concentró bajo presión reducia y se purificó mediante cromatografía sobre gel de sílice (95:5 de DCM/MeOH) para dar 0,014 g del sólido blanco.

Rendimiento= 30%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,23-1,38 (m, 4H), 1,76-1,86 (m, 4H), 2,06 (s, 3H), 2,45-2,60 (m, 1H), 4,52 (d, 1H), 3,38-3,44 (m, 1H), 3,47 (m, 3H), 7,58 (d, 2H), 7,68 (d, 2H), 10,15 (s, 1H).

MS (m/z) / M+1 = 346,87

HPLC (pureza uv, λ= 214 nm)= 98,5%

Ejemplo I87: R_1= (1R*,3S*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-acetilamino-fenilo

N-{4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida

I87 se preparó mediante el procedimiento descripto en el ejemplo I86 (protocolo A).

I87 se purificó mediante cromatografía sobre gel de sílice con AcOEt:Ciclohexano (80:20) y se lavó con MeOH para dar 0,15 g del compuesto esperado.

Rendimiento= 20%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,10-1,30 (m, 4H), 1,55-2,00 (m, 4H), 2,10 (s, 3H), 2,60 (m, 1H), 3,50 (m, 1H), 3,50 (s, 3H), 4,6 (d, 1H), 7,60 (dd, 2H), 7,60 (dd, 2H), 10,15 (s,1H).
M+1 = 347,1

Ejemplo I88: R_1= (1R*,3R*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-acetilamino-fenilo

N-{4-[5-((1R*,3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida

A una suspensión de I87 (0,4 mmol, 0,15 g) en DCM (2 ml) que contenía tamices moleculares de 4A (0,216 g), óxido de N-morfolina (0,65 mmol, 0,76 g) bajo una atmósfera de nitrógeno se agregó perrutenato de tetrapropilamonio (10% equivalente en moles, 15 mg). La mezcla resultante se agitó toda la noche, se filtró, se lavó con metanol y se concentró bajo presión reducida. El residuo se purificó por cromatografía sobre gel de sílice con DCM/MeOH (95:5) para dar 0,1 g de una cetona intermedia: N-{4-[4-metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida.
Rendimiento= 71%
^{1}H-NMR (400MHz, DMSO) δ ppm: 1,25 (m, 1H), 1,60-1,75 (m, 2H), 1,85-2 (m, 2H), 2,05 (s, 3H), 2,3 (m, 3H), 3,15 (m, 1H), 3,5 (s, 3H), 7,55 (dd, 2H), 7,70 (dd, 2H), 10,15 (s,1H).

A una solución de este intermedio de cetona (0,15 mmol, 0,05 g) en THF (2 ml) a -70°C bajo una atmósfera de nitrógeno se agregó una solución de 1M de L-Selectride en THF (0,2 mmol, 0,2 ml). La mezcla resultante se dejó calentar a temperatura ambiente durante 1 hora, se diluyó con diclorometano, se lavó con éter y se concentró bajo presión reducida. El residuo se purificó por cromatografía sobre gel de sílice AcOEt:Ciclohexano (80:20) para dar 30 mg del producto esperado.

Rendimiento = 60%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,25-1,30 (m, 3H), 1,72-1,78 (m, 5H), 2,20 (s, 3H), 3,11-3,14 (m, 1H), 3,58 (s, 3H), 4,13 (m, 1H), 7,20 (s, 1H), 7,52-7,60 (m, 4H).

MS (m/z) / M+1= 347,21

HPLC (pureza uv, λ= 214 nm)= 98%

Ejemplo I89: R_1= (1R*,3R*)-3-hidroxi-ciclohexilo, R_2= metilo, R_3= 4-acetilamino-piridin-3-ilo

N-{5-[5-((1R*,3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-piridin-2-il}-acetamida

El compuesto I89 se preparó mediante el procedimiento descripto en el ejemplo I4 (protocolo A).

A una suspensión de perclorato de 1,3,4-tiadiazolio (3e) (0,5 mmol, 2 g) en etanol (20 ml) se agregaron trietilamina (1,5 mmol, 2 ml) y luego 3-aminociclohexanol (0,8 mmol, 0,9 ml) y la mezcla se mantuvo a 70°C toda la noche, se concentró bajo presión reducida. El residuo se recogió en diclorometano, se lavó dos veces con agua, se concentró bajo presión reducida y se purificó por cromatografía sobre gel de sílice (20:80 ciclohexano/EtOAc) para dar 0,03 g del sólido blanco.

Rendimiento= 17%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,37-1,65 (m, 8H), 2,11 (s, 3H), 3,03-3,08 (m, 1H), 3,50 (s, 3H), 3,91-3,92 (m, 1H), 4,41 (d, 1H), 8,01-8,03 (dd, 1H), 8,17 (d, 1H), 8,55 (d, 1H), 10,75 (s, 1H).

MS (m/z) / M+1= 348,3

HPLC (pureza uv, λ= 214 nm)= 99,2%

Ejemplo I90: R_1= 3-ciano-fenilo, R_2= metilo, R3= 4-cloro-fenilo

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzonitrilo

A una suspensión de I6.11 (4,14 mmol, 1,43 g) en piridina (20 ml), se agregó cloruro de benzoilo (8,28 mmol, 964 µl). La mezcla se calentó a reflujo durante 20 días.

El solvente se concentró bajo presión reducida, la mezcla de la reacción se recogió nuevamente en una solución acuosa de $NaHCO_3$ y el producto crudo se extrajo con diclorometano. El compuesto se purificó mediante cromatografía sobre gel de sílice (eluido con ciclohexano/acetato de etilo de 80/20 a 70/30) para dar 1,25 g del compuesto esperado (92%).

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,8 (s, 3H), 7,40 (d, 1H), 7,48 (s, 1H), 7,52-7,60 (m, 4H), 7,73 (d, 2H).

MS (m/z) / M+1= 327/329

HPLC (pureza uv, λ= 245nm)= 99,4%

Ejemplo I90.1: R_1= 3-(1H-Tetrazol-5-il)-fenilo, R_2= metilo, R_3= 4-cloro-fenilo

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina

Una mezcla de I90 (1,22 mmol, 0,4 g), azida de sodio (1,59 mmol, 0,1 g) y clorhidrato de trietilamina (1,59 mmol, 0,22 g) en tolueno (7 ml) se calentó a 90°C con agitación bajo una atmósfera de nitrógeno. Después de enfriar, la mezcla de la reacción se vertió en agua y se extrajo con diclorometano. A la capa acuosa, se agregó HCl acuoso 0,1N hasta el pH sea ácido (¡ATENCIÓN! Esto se debe hacer debajo de una campana bien ventilada). El precipitado se filtró, se lavó con éter y el compuesto resultante se cristalizó en diclorometano que

contenía pocas gotas de metanol para dar 0,1 g del compuesto deseado.

Rendimiento: 24%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,8 (s, 3H), 7,28 (d, 1H), 7,55 (d, 2H), 7,60 (t, 1H), 7,70-7,77 (m, 4H)

MS (m/z) / M+1 = 370/372

HPLC (pureza uv, λ= 245 nm)= 99,7%

Ejemplo I90.2: R_1= 3-(N-Hidroxicarbamimidoil)-fenilo, R_2= metilol, R_3= 4-cloro-fenilo

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-N-hidroxi-benzamidina

A una mezcla de I90 (1,53 mmol, 0,5 g) y clorhidrato de hidroxilamina (2,29 mmol, 0,156 g) en etanol (13 ml) se agregó hidróxido de sodio (2,29 mmol, 0,09 g) disuelto en el mínimo de agua. La mezcla de la reacción se calentó a reflujo durante 24 h con agitación. Después de enfriar, el precipitado se filtró, se lavó con etanol y se secó bajo vacío a 45°C para dar 0,54 g del compuesto deseado.

Rendimiento: 98%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,8 (s, 3H), 5,76 (bs, 2H), 7,05 (dd, 1H), 7,34-7,4 (m, 3H), 7,54 (d, 2H), 7,70 (d, 2H), 9,6 (s, 1H).

MS (m/z) / M+1= 360/362

HPLC (pureza uv, λ= 245 nm)= 97,3%

Ejemplo I90.3: R_1= 3-(5-hidroxi-[1,2,4]oxadiazol-3-il)-fenilo, R_2= metilo, R_3= 4-cloro-fenilo

3-{3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-[1,2,4]oxadiazol-5-ol

Una mezcla de I90.2 (2,78 mmol, 0,1 g) y 1,1'-carbonildiimidazol (5,56 mmol, 0,9 g) en THF anhidro (2 ml) se calentó a reflujo durante 5 h. Después de enfriar, la mezcla de la reacción se concentró y se vertió en agua. Se agregó diclorometano y el precipitado se filtró y se lavó con metanol. La mezcla resultante se purificó mediante cromatografía sobre gel de sílice (diclorometano/metanol eluyente: 98/2 + 1% de ácido acético) para dar 0,03 g del producto deseado.

Rendimiento: 28%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,8 (s, 3H), 7,20 (dt, 1H), 7,50-7,55(m, 5H), 7,70 (d, 2H).

MS (m/z) / M+1 = 386/388

HPLC (pureza uv, λ= 245 nm)= 98,2%

EJEMPLO I: PROTOCOLO C

Ejemplo I91: R_1= ciclohexilo, R_2= metilo, R_3= 3-metil-4-bromo-fenilo

[5-(4-Bromo-3-metil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

I91 se preparó mediante el procedimiento descripto en el ejemplo I18 (Protocolo C) usando los intermedios y reactivos apropiados.

Rendimiento= 50,4%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,21-1,51 (m, 5H), 1,64-1,70 (m, 1H), 1,78-1,89 (m, 4H), 2,38 (s, 3H), 2,56-2,64 (m, 1H), 3,55 (s, 3H), 7,28 (d, 1H), 7,47 (s, 1H), 7,54 (d, 1H).

MS (m/z) / M+1= 366/368

Ejemplo I91.1: R_1= ciclohexilo, R_2= metilo, R_3= 3-metil-4-ciano-fenilo

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzonitrilo

A una solución de I91 (7,370 mmol, 2,7 g) en N-metil-2-pirrolidona (17 ml), se agregó cianuro de cobre (13,267 mmol, 1,19 g) y la mezcla se calentó a reflujo durante 3 h. La mezcla se enfrió a temperatura ambiente, se basificó con una solución de amoníaco acuoso (2N) y se agitó durante 10 h a temperatura ambiente. La suspensión se filtró luego a través

de Celita y la capa acuosa se extrajo con acetato de etilo, se lavó con agua y solución salina, se secó ($MgSO_4$), se filtró y luego se concentró bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice, eluyendo con un gradiente de diclorometano que contenía del 0% al 1% de metanol.

Rendimiento= 54,8

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,22-1,59 (m, 5H), 1,64-1,67 (m, 1H), 1,77-1,87 (m, 4H), 2,57-2,67 (m, 4H), 3,60 (s, 3H), 7,52 (d, 1H), 7,56 (s, 1H), 7,63 (d, 1H).

Ejemplo I91.2: R_1= ciclohexilo, R_2= metilo, R_3= 3-metil-4-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzamida

A una solución de I91.1 (0,320 mmol, 0,1 g) en etanol (17 ml), se agregaron una solución de carbonato de sodio 3N (3,424 mmol, 1,14 ml) luego una solución de peróxido de hidrógeno (5,60 ml). La suspensión se agitó durante 2 días a temperatura ambiente, luego se calentó a 40°C durante 8 h. La mezcla se vertió en una solución de $Na_2S_2O_5$ y se evaporó hasta secarse, luego el material crudo se diluyó con agua y se extrajo con diclorometano. La capa orgánica se lavó con agua y solución

salina, se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida.

Rendimiento= 70%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,22-1,51 (m, 5H), 1,60-1,68 (m, 1H), 1,81-1,91 (m, 4H), 2,52 (s, 3H), 2,59-2,69 (m, 1H), 3,60 (m, 3H), 5,64-5,83 (b, 2H), 7,49 (s, 2H), 7,48 (s, 1H).

MS (m/z) / M+1= 331/332.

HPLC (pureza uv, λ= 214 nm): 97,28%

Ejemplo I92: R_1= ciclohexilo, R_2= metilo, R_3= 4-bromo-3-metoxi-fenilo

[5-(4-Bromo-3-metoxi-fenil)-3-metil-2,3-dihidro-[1,3,4]tiadiazol-2-il]-ciclohexil-amina

A una mezcla de ácido 3-hidroxámico (14,480 mmol, 2 g) en ácido acético (14,5 ml) y ácido sulfúrico (1,5 ml) a 50°C, se agregó una solución de bromo (15,204 mmol, 0,780 ml) en ácido acético (7,2 ml) y se agitó durante 30 minutos a 100°C. La reacción se dejó a temperatura ambiente y se diluyó con agua. La capa acuosa se extrajo con acetato de etilo, se lavó con agua y solución salina, se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida para dar el ácido 4-bromo-2-hidroxi-benzoico (rendimiento = 100%).

A una solución de ácido 4-bromo-3-hidroxibenzoico (14,480 mmol, 2,600 g) en acetona (180 ml), se agregaron carbonato de potasio (62,988 mmol, 8,710 g) y sulfato de dimetilo (31,422 mmol, 2,970 ml). La reacción se agitó a temperatura ambiente durante 30 minutos y se avaporó hasta secarse. El residuo luego se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica recogida se lavó con agua y solución salina, se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. El metil éster del ácido 4-bromo-3-metoxi-benzoico se aisló mediante cromatografía sobre gel de sílice eluyendo con ciclohexano que contenía del 0% al 20% de acetato de etilo (rendimiento= 47%).

A una solución de metil éster del ácido 4-bromo-3-metoxi-benzoico (6,875 mmol, 1,676 ml) en una mezcla 1/1 de THF/MeOH (15 ml), se agregó hidróxido de litio (7,553 mmol, 0,180 g) y la reacción se agitó a temperatura ambiente toda la noche antes de la destilación de volátiles. El residuo se diluyó con agua, se acidificó con una solución de HCl (1N) y se agitó durante 1 h. El precipitado formado se filtró, se lavó con agua y éter de petróleo para dar ácido 4-bromo-3-metoxi-benzoico (Rendimiento = 56%).

El compuesto del título se preparó mediante el procedimiento descripto en el ejemplo I17 (protocolo C) comenzando desde el

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ácido 4-bromo-3-metoxi-benzoico. En este caso particular, se agregó metiltrifluorometanosulfonato (1,2 eq) una vez y la capa acuosa básica se extrajo con DCM. El producto crudo se cromatografió sobre gel de sílice eluyendo con ciclohexano que contenía del 0% al 10% de acetato de etilo. El aceite obtenido se trituró en dietil éter y el sólido blanco formado se aisló mediante filtración.

Rendimiento= 26% (en total, los 2 pasos)

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,46 (m, 5H), 1,60-1,68 (m, 1H), 1,77-1,88 (m, 4H), 2,58-2,68 (m, 1H), 3,59 (s, 3H), 3,96 (s, 3H), 7,02 (d, 1H), 7,22 (s, 1H), 7,53 (d, 1H)

Ejemplo I92.1: R_1= cilohexilo, R_2= metilo, R_3= 3-metoxi-4-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-benzamida

I92 reaccionó con cianuro de cobre mediante el procedimiento descripto en el ejemplo I91-1 y el intermedio formado se transformó en I92.1 siguiendo el siguiente protocolo:

A una solución heterogénea de este material (0,9134 mmol, 0,300 g) en etanol (50 ml), se agregaron una solución de carbonato de sodio (3N) (9,773 mmol, 3,258 ml) y peróxido de hidrógeno (13,3 ml) y la reacción se calentó a 40°C durante 1,5 días. La mezcla se vertió en una solución saturada de

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$Na_2S_2O_5$ y la solución se concentró bajo presión reducida. El residuo se diluyó con agua, se extrajo con diclorometano y la capa orgánica se lavó con agua y solución salina, se secó sobre $MgSO_4$, se filtró y luego se evaporó hasta secarse. El material crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con diclorometano que contenía del 0% al 4% de metanol.

Rendimiento: 25%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,50 (m, 5H), 1,76-1,88 (m, 4H), 2,59-2,69 (m, 1H), 3,60 (s, 3H), 4,02(s, 3H), 5,80-5,90 (b, 1H), 7,25 (d, 1H), 7,34 (s, 1H), 7,62-7,67 (b, 1H), 8,23 (d, 1H).

MS (m/z) / M+1= 347/348

HPLC (pureza uv, λ= 214 nm): 97,61%

Ejemplo I92.2: R1= ciclohexilo, R_2= metilo, R_3= 3-hidroxi-4-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-hidroxi-benzamida

A una mezcla de I92.1 y yoduro de n-tetrabutilamonio (0,433 mmol, 0,160 g) en diclorometano anhidro (2 ml) bajo una atmósfera de nitrógeno a -78°C, se agregó una solución de BCl_3 1N en diclorometano (0,433 mmol, 0,433 ml) y la mezcla de la reacción se dejó agitar a -78°C durante 10 minutos y luego

durante 2 h a 0°C y 1h30 a temperatura ambiente. Luego, se agregó una solución de BCl_3 1N en diclorometano (0,433 mmol, 0,433 ml). Después de 1h30 adicional de agitación a temperatura ambiente, la reacción se enfrió con agua y se basificó con una solución saturada de bicarbonato de sodio antes de la extracción con diclorometano. La capa orgánica se lavó con solución salina, se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse. El residuo se cromatografió sobre gel de sílice eluyendo con diclorometano que contenía del 0% al 4% de metanol para dar el producto deseado.

Rendimiento= 26%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,21-1,50 (m, 5H), 1,63-1,70 (m, 1H), 1,80-1,90 (m, 4H), 2,58-2,68 (m, 1H), 3,60 (s, 3H), 5,70-6,20 (b, 2H), 7,18 (s, 1H), 7,24 (d, 1H), 7,38 (d, 1H), 12,25 (s, 1H).

MS (m/z) / M+1= 333/334

HPLC (pureza uv, λ= 214 nm): 96,54%

Ejemplo I93: R_1= ciclohexilo, R_2= metilo, R_3= 3-nitro-4-metoxicarbonil-fenilo

Metil éster del ácido 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-nitro-benzoico

I93 se preparó mediante el procedimiento descripto en el ejemplo I21 (protocolo C) usando los intermedios y reactivos apropiados. En este caso particular, no se usó trietilamina y el producto esperado se aisló mediante filtración después del tratamiento con una solución saturada de $NaHCO_3$.

Rendimiento= 77%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,48 (m, 5H), 1,64-1,70 (m, 1H), 1,80-1,90 (m, 4H), 5,58-5,66 (m, 1H), 3,63 (s, 3H), 3,82 (s, 3H), 7,80-7,84 (m, 2H), 8,11 (s, 1H).

Ejemplo I93.1: R_1= ciclohexilo, R_2= metilo, R_3= 3-amino-4-metoxicarbonil-fenilo

Metil éster del ácido 2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

A una solución de I93 (0,328 mmol, 0,500 g) en etanol (20 ml), se agregó cloruro de estaño dihidratado (6,641 mmol, 1,495 g) y la mezcla se calentó a reflujo durante 5 h, luego se dejó en reposo a temperatura ambiente toda la noche. La mezcla se evaporó hasta secarse y el material crudo se basificó con una solución saturada de carbonato de sodio antes de la extracción con diclorometano. La capa orgánica se lavó con solución salina, se secó sobre $MgSO_4$, se filtró y se concentró bajo vacío. El residuo se se cromatografió sobre gel de sílice

eluyendo con diclorometano que contenía del 0% al 2% de metanol para dar el compuesto deseado.

Rendimiento= 65%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,21-1,49 (m, 5H), 1,60-1,69 (m, 1H), 1,80-1,90 (m, 4H), 2,58-2,67 (m, 1H), 3,60 (s, 3H), 3,89 (s, 3H), 5,77-5,83 (b, 2H), 7,88-7,92 (m, 2H), 7,89 (d, 1H).

MS (m/z) / M+1= 347/349

HPLC (pureza uv, λ= 214 nm): 98,31%

Ejemplo I93.2: R_1= ciclohexilo, R_2= metilo, R_3= 3-acetilamino-4-metoxicarbonil-fenilo

Metil éster del ácido 2-Acetilamino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

A una suspensión de I93.1 (0,144 mmol, 0,05 g) en tolueno anhidro (2 ml) a 0°C, se agregaron trietilamina (0,150 mmol, 0,015 ml) y anhídrido acético (0,160 mmol, 0,015 ml). La reacción se dejó agitar a temperatura ambiente durante 3 días y se agregaron 5,4 equivalentes más de anhídrido acético y trietilamina. Después de 2 días de agitación a temperatura ambiente, la mezcla se evaporó hasta secarse y el residuo se cromatografió sobre gel de sílice eluyendo con diclorometano que contenía del 0% al 1% de metanol.

Rendimiento= 89%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,21-1,49 (m, 5H), 1,60-1,67 (m, 1H), 1,76-1,88 (m, 4H), 2,28 (s, 3H), 2,60-2,70 (m, 1H), 3,60 (s, 3H), 3,93 (s, 3H), 7,45 (d, 1H), 8,03 (d, 1H), 8,98 (s, 1H), 11,10 (s, 1H).

MS (m/z) / M+1= 389/390

HPLC (pureza uv, λ=214 nm): 96,93%

Ejemplo I93.3: R_1= ciclohexilo, R_2= metilo, R_3= 3-amino-4-benzamida

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

I93 se modificó siguiendo el procedimiento descripto en el ejemplo I37.3 para dar el derivado de amida con un rendimiento general del 84%. La reducción del grupo nitro para dar I93.3 se realizó como se describió en el ejemplo I93.1. En este caso particular, la mezcla de la reacción se basificó con un una solución saturada de carbonato de sodio luego se destiló. El producto crudo se diluyó en agua y se extrajo con diclorometano. La fase acuosa, saturada con solución salina, se extrajo luego con acetato de etilo y la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse para dar un residuo que se purificó mediante dos cromatografías consecutivas sobre gel de sílice, eluyendo primero con

diclorometano/metanol (93/7) y la segunda purificación se hizo eluyendo con un gradiente de ciclohexano que contenía del 0% al 40% de acetato de etilo.

Rendimiento= 10%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,27-1,40 (m, 5H), 1,56-1,62 (m, 1H), 1,70-1,80 (m, 4H), 2,58-2,65 (m, 1H), 3,50 (s, 3H), 6,73-6,78 (m, 3H), 7,00 (s, 1H), 7,10-7,20 (b, 1H), 7,61 (d, 1H), 7,75-7,85 (b, 1H).

MS (m/z) / M+1= 332/333

HPLC (pureza uv, λ= 214 nm): 95,83%

Ejemplo I93.4: R_1= ciclohexilo, R_2= metilo, R_3= 4-oxo-3,4-dihidro-quinazolin-7-ilo

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona

Una mezcla de I93.1 (1,443 mmol, 0,500 g) y formamida (4 ml) se agitó y se calentó a reflujo durante 2 h antes de enfriar a temperatura ambiente. La mezcla se diluyó con agua y el precipitado se recogió mediante filtración. El precipitado se lavó con agua y éter de petróleo y se purificó mediante cromatografía sobre gel de sílice, eluyendo con diclorometano que contenía del 0% al 3% de metanol seguida por la elución isocrática con diclorometano/metanol (93/7).

00830

Rendimiento= 20%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,40 (m, 5H), 1,55-1,64 (m, 1H), 1,70-1,83 (m, 4H), 2,63-2,71 (m, 1H), 3,56 (s, 3H), 7,73 (s, 1H), 7,00 (s, 1H), 7,80 (d, 1H), 8,12-8,19 (m, 3H), 12,30-12,40 (b, 1H).

MS (m/z) / M+1= 342/343

HPLC (pureza uv, λ= 214 nm): 95,19%

Ejemplo I93.5: R_1= ciclohexilo, R_2= metilo, R_3= 4-amino-quinazolin-7-ilo

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina

Una mezcla de I93.4 (0,264 mmol, 0,090 g), cloruro de tionilo (2 ml) y una cantidad catalítica de dimetilformamida se refluyó durante 2 h antes de la destilación de los solventes bajo presión reducida. Al residuo, se agregó una solución de NH_3 (0,5N) en dioxano (4 ml) y la mezcla se calentó en un tubo sellado a 80°C durante 4 días. La mezcla luego se evaporó hasta secarse y el producto crudo se diluyó en una solución de ácido acético (0,1 ml de AcOH en 10 ml de H_2O), y se extrajo con diclorometano para remover las impurezas. La fase acuosa luego se basificó con una solución de NaOH (0,1N) y luego se extrajo con diclorometano. La fase orgánica se lavó con agua,

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solución salina, se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida para dar el producto deseado.

Rendimiento= 7,5%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,29-1,50 (m, 5H), 1,60-1,69 (m, 1H), 1,79-1,90 (m, 4H), 2,65-2,72 (m, 1H), 3,65 (s, 3H), 5,60-5,70 (b, 2H), 7,75 (d, 1H), 7,90 (s, 1H), 7,98 (d, 1H), 8,67 (s, 1H).

MS (m/z) / M+1= 341/343

HPLC (pureza uv, λ= 214 nm): 99,99%

Ejemplo I93.6: R_1= ciclohexilo, R_2= metilo, R_3= 2,4-Dioxo-1,2,3,4-tetrahidro-quinazolin-7-ilo

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-1H-quinazolin-2,4-diona

A una solución de I93.3 en THF (4 ml), se agregó carbonildiimidazol (0,464 mmol, 0,080 g) y la reacción se calentó a reflujo toda la noche. Se agregó carbonildiimidazol (0,464 mmol, 0,080 g) y la mezcla se mantuvo a reflujo durante 24 h. Luego, el solvente se destiló y el residuo se purificó mediante cromatografía sobre gel de sílice, eluyendo con un gradiente de ciclohexano que contenía del 15% al 30%. El producto cromatografiaado se solubilizó en acetato de etilo y la capa orgánica se lavó con agua. La capa orgánica recogida

se lavó con solución salina, se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse para dar el producto del título.

Rendimiento= 13,3%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,28-1,39 (m, 5H), 1,56-1,64 (m, 1H), 1,72-1,82 (m, 4H), 2,62-2,67 (m, 1H), 3,54 (s, 3H), 7,41-7,43 (m, 2H), 7,94 (d, 1H), 11,17 (s, 1H), 11,36 (s, 1H).

MS (m/z) / M+1 = 358/359

HPLC (pureza uv, λ= 214 nm): 96,70%

Ejemplo I94: R_1= ciclohexilo, R_2= metilo, R_3= 3-metoxi-4-sulfamoil-fenilo

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencensulfonamida

El compuesto del título se preparó mediante el procedimiento descripto en el ejemplo I19 (protocolo C) usando los intermedios y reactivos apropiados. El residuo se purificó mediante cromatografía sobre gel de sílice, eluyendo con diclorometano que contenía del 0% al 2% de metanol.

Rendimiento= 59%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,21-1,49 (m, 5H), 1,63-1,69 (m, 1H), 1,77-1,87 (m, 4H), 2,59-2,67 (m, 1H), 3,60 (s, 3H), 4,06 (s, 3H), 5,02 (s, 2H), 7,20 (d, 1H), 7,40 (s, 1H), 7,90 (d, 1H).

MS (m/z) / M+1 = 384/386

HPLC (pureza uv, λ= 214 nm): 99,99%

Ejemplo I95: R_1= ciclohexilo, R_2= metilo, R_3= 4-metoxi-3-sulfamoil-fenilo

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencensulfonamida

El compuesto del título se preparó mediante el procedimiento descripto en el ejemplo I18 (protocolo C) usando los intermedios y reactivos apropiados.

En este caso particular, el residuo obtenido después de la extracción y la destilación se trituró con metanol y el precipitado se filtró y se purificó mediante cromatografía sobre gel de sílice, eluyendo con una mezcla de ciclohexano/acetato de etilo (1/1).

Rendimiento= 9%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,30-1,50 (m, 5H), 1,62-1,70 (m, 1H), 1,80-1,90 (m, 4H), 2,58-2,65 (m, 1H), 3,58 (s, 3H), 4,02 (s, 3H), 5,10 (s, 2H), 7,09 (d, 1H), 7,80 (d, 1H), 8,12 (s, 1H).

MS (m/z) / M+1 = 383/384

HPLC (pureza uv, λ= 214 nm): 99,38%

Ejemplo I96: R_1= 3-metoxicarbonil-fenilo, R_2= metilo, R_3= 3-ciano-fenilo

Metil éster del ácido 3-[5-(3-Ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

A una solución de 7j (1,25 mmol, 0,42 g) en dioxano anhidro (14 ml), se agregó sulfonato de metiltrifluorometano (1,5 mmol, 142 µl). La mezcla resultante se agitó durante 24 h a temperatura ambiente. A esta solución se agregó sulfonato de metiltrifluorometano (0,45 mmol, 43 µl) para asegurar que se complete la reacción. El solvente se removió mediante la destilación bajo presión reducida para dar un material crudo que se basificó con una solución saturada de $NaHCO_3$ y se extrajo con diclorometano. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El material crudo se purificó mediante 2 cromatografías rápidas sucesivas (eluyente: diclorometano/metanol de 95/5 y ciclohexano/acetato de etilo de 90/10) para dar el compuesto deseado, 0,23 g (rendimiento del 53%).

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,75 (s, 3H), 3,86 (s, 3H), 7,34(d, 1H), 7,54 (t, 1H), 7,61 (s, 1H), 7,67-7,70 (m, 2H), 7,94 (d, 1H), 8,02 (d, 1H), 8,12(s, 1H).

MS (m/z) / M+1: 351/353

Ejemplo I96.1: R_1= ácido 3-benzoico, R_2= metilo, R_3= 3-ciano-fenilo

Ácido 3-[5-(3-Ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

Una mezcla de I96 (3 mg, 8,56 mmol) e hidróxido de potasio (1N en agua, 12,8 mmol, 12,8 ml) en tetrahidrofurano (90 ml) se agitó a temperatura ambiente toda la noche. La mezcla de la reacción se calentó a reflujo durante 1 h. Después de enfriar, la mezcla de la reacción se concentra, se agrega agua (2 ml) y se agrega una solución de HCl (1N en agua, 12,8 mmol, 12,8 ml). El precipitado se recoge mediante filtración y se lava sucesivamente con agua y con éter antes de ser secado bajo vacío a 45°C. El compuesto se purificó mediante cromatografía rápida (eluyente: diclorometano/metanol 99/1 +1% de ácido acético) para dar 2,38 g del producto del título.

Rendimiento: 83%

^{1}H-NMR (400 MHz, DMSO) δ ppm : 3,8 (s, 3H), 7,31 (d, 1H), 7,51 (t, 1H), 7,61 (s, 1H), 7,65-7,69 (m, 2H), 7,93 (d, 1H), 8,01 (d, 1H), 8,11 (s, 1H), 13,06 (s, 1H).

MS (m/z) / M+1 = 337/338

HPLC (pureza uv, λ= 245 nm): 99,6%

Ejemplo I97: R_1= 3-metoxicarbonil-fenilo, R_2= metilo, R_3= 2-poridilo

Metil éster del ácido 3-[3-Metil-5-piridin-2-il-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

A una solución de 7k (1,76 mmol, 0,55 g) en dioxano anhidro (14 ml) y trietilamina (1,76 mmol, 264 µl), se agregó sulfonato de metiltrifluorometano (1,76 mmol, 199 µl). La mezcla resultante se agitó durante 24 h. A esta solución se agregó sulfonato de metiltrifluorometano (0,53 mmol, 60 µl) y trietilamina (0,53 mmol, 79,2 µl) para permitir que la reacción se complete. El solvente se removió mediante la destilación bajo presión reducida para dar un material crudo que se basificó con una solución saturada acuosa de $NaHCO_3$ y se extrajo con diclorometano. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El material crudo se purificó mediante filtración sobre gel de sílice (eluyente: diclorometano) para dar el compuesto deseado.

Rendimiento: 28%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,76 (s, 3H), 3,86 (s, 3H), 7,35 (dd, 1H), 7,48-7,54 (m, 2H), 7,64-7,68 (m, 2H), 7,96-8,00 (m, 2H), 8,58 (d, 1H).

MS (m/z) / M+1: 327/329

Ejemplo I97.1: R_1 = ácido 3-benzoico, R_2= metilo, R_3= 2-piridilo

Ácido 3-[3-Metil-5-piridin-2-il-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

Una mezcla de I97 (16 g, 0,49 mmol) e hidróxido de potasio (1N en agua, 0,58 mmol, 0,58 ml) en tetrahidrofurano (3 ml) se agitó a temperatura ambiente durante 48 h. La mezcla de la reacción se calentó a reflujo durante 2 h. Después de enfriar, la mezcla de la reacción se concentró, se agregó agua (5 ml), la capa acuosa se extrajo con diclorometano y se neutralizó con una solución de HCl (0,1 N en agua). El precipitado se recogió mediante la filtración y se lavó sucesivamente con agua y con éter antes de ser secado bajo vacío a 45°C para dar 0,08 g del producto del título.

Rendimiento: 54%

^{1}H-NMR (400 MHz, DMSO) δ ppm: 3,8 (s, 3H), 7,31 (d, 1H), 7,47-7,49 (m, 2H), 7,64-7,66 (m, 2H), 7,96-7,98 (m, 2H), 8,58 (d, 1H)

MS (m/z) / M+1= 313/314/315

HPLC (pureza uv, λ= 245 nm): 97,6%

Ejemplo I98: R_1= ácido 3-benzoico, R_2= metilo, R_3= 4-Cloro-3-sulfamoil-fenilo

Ácido 3-[5-(4-Cloro-3-sulfamoil-fenilo)-3-metilo-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico

I98 se preparó mediante el procedimiento descripto en el ejemplo I96.1 usando los intermedios y reactivos apropiados. En este caso particular, el intermedio éster se basificó con trietilamina. El producto del título se aisló mediante cromatografía sobre gel de sílice, eluyendo con acetato de etilo/ciclohexano (15/85).

Rendimiento = 19% (2 pasos)

^{1}H-NMR (400MHz, DMSO) δ ppm: 3,73 (s, 3H), 3,85 (s, 3H), 7,35 (d, 1H), 7,54 (t, 1H), 7,62 (s, 1H), 7,70-7,80 (m, 4H), 7,86 (d, 1H), 8,24 (s, 1H).

MS (m/z) / M+1 = 439/441

Luego, una solución (1N) de hidróxido de potasio (1,139 mmol, 1,14 ml) se agregó a una solución del derivado de éster (0,456 mmol, 0,2 g) en THF (5 ml) y la mezcla se agitó toda la noche. La mezcla de la reacción se evaporó hasta secarse y el residuo se diluyó en etanol y se acidificó con una solución (6,9 N) de HCl en etanol (0,165 ml). La mezcla se agitó a RT durante 5 h y el solvente se destiló bajo presión reducida. El material crudo se cromatografió sobre gel de sílice, eluyendo con un gradiente de diclorometano que contenía del 5% al 25% de metanol. El producto aislado se solubilizó en THF y se filtró a través de un tampón de gel de sílice y el filtrado se evaporó hasta secarse para dar el producto deseado.

Rendimiento= 27%

^{1}H-NMR (400MHz, CDCl3) δ ppm: 3,74 (s, 3H), 7,24 (d, 1H), 7,45 (t, 1H), 7,62 (s, 1H), 7,66 (d, 1H), 7,73-7,80 (m, 3H), 7,84 (d, 1H), 8,23 (s, 1H).

MS (m/z) / M+1= 425/427

HPLC (pureza uv, λ= 214 nm): 94,86%

EJEMPLO I: PROTOCOLO D

Ejemplo I99: R_1= ciclohexilo, R_2= metilo, R_3= 4-ciano-fenilo

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo

El compuesto I99 se preparó mediante el procedimiento descripto en el ejemplo I15 (protocolo D).

A una mezcla de ácido 4-cianobenzoico (74,8 mmol, 11 g), 2-metiltiosemicarbazida 5a (74,8 mmol, 13,42 g) en dioxano anhidro (110 ml) a 70°C, se agregó $POCl_3$ (89,65 mmol, 76,76 ml) y la mezcla se calentó a 95°C durante 4 horas. El solvente se removió mediante destilación bajo presión reducida para dar un material crudo que se basificó a pH 8-7 con una solución saturada de $NaHCO_3$. La fase acuosa se extrajo con diclorometano. La capa orgánica se lavó con agua y una solución saturada de NaCl, se secó sobre sulfato de magnesio,

se filtró y se destiló para dar un residuo que se purificó cromatografía sobre gel de sílice (eluido con un gradiente de ciclohexano/acetato de etilo que terminó con la razón de 90/10) para dar 8,5 g del compuesto del título.

Rendimiento: 42%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,40 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,83 (m, 4H), 2,57-2,70 (m, 1H), 3,55 (s, 3H), 7,82 (dd, 2H), 7,93 (dd, 2H).

Ejemplo I99.1: R_1= ciclohexilo, R_2= metilo, R_3= 4-(1H-tetrazol-5-il)-fenilo

Ciclohexil-{3-metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-iliden}-amina

A una solución de I99 (1,67 mmol, 500 mg) en tolueno (2 ml), se agregó azida de sodio (2,18 mmol, 142 mg), clorhidrato de trietilamina (2,18 mmol, 300 mg) y la mezcla se calienta a reflujo durante 24 horas. La mezcla de la reacción se enfrió a temperatura ambiente, se acidificó con una solución de HCl [0,1N], y luego se basificó a pH=6-7 con una solución saturada de $NaHCO_3$. La fase acuosa se extrajo con acetato de etilo y la capa orgánica se lavó con una solución saturada de NaCl, se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida. El residuo se cromatografió sobre una columna de gel de sílice usando un gradiente de diclorometano

que contenía del 0% al 20% de metanol para dar el compuesto del título.

Rendimiento: 61%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,42 (m, 5H), 1,55-1,65 (m, 1H), 1,70-1,85 (m, 4H), 2,60-2,72 (m, 1H), 3,55 (s, 3H), 7,85 (dd, 2H), 8,13 (dd, 2H)

MS (m/z) / M+1= 341/342

HPLC (pureza uv, λ = 214 nm)= 99,9%

Ejemplo I100: R_1= ciclohexilo, R_2= metilo, R_3= 4-nitro-fenilo

Ciclohexil-[3-metil-5-(4-nitro-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina

I100 se preparó como se describió en el ejemplo I15 (protocolo D) usando los reactivos apropiados. El material crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexano que contenía del 0% al 10% de acetato de etilo.

Rendimiento: 40%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,20-1,40 (m, 5H), 1,57-1,64 (m, 1H), 1,72-1,83 (m, 4H), 2,61-2,91 (m, 1H), 3,56 (s, 3H), 7,89 (d, 2H), 8,29 (d, 2H).

MS (m/z) / M+1 = 319/320

Ejemplo I100.1: R_1= ciclohexilo, R_2= metilo, R_3= 4-amino-fenilo

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenilamina

Cloruro de etaño dihidratado (93,278 mmol, 20,987 g) se agregó a una solución de I100 (18,656 mmol, 5,940 g) en etanol a 70°C y la mezcla se refluyó durante 1h30. La mezcla luego se filtró sobre Celita y el filtrado se evaporó hasta secarse. El material crudo se basificó con una solución saturada de bicarbonato de sodio, luego se extrajo con acetato de etilo. La capa orgánica se lavó con agua y solución salina, se secó sobre $MgSO_4$, se filtró y luego se evaporó hasta secarse. El residuo se filtró a través de un tampón de gel de sílice con una mezcla de diclorometano/metanol (95/5).

Rendimiento= 62%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,19-1,37 (m, 5H), 1,56-1,63 (m, 1H), 1,70-1,80 (b, 4H), 2,56-2,74 (m, 1H), 3,44 (s, 3H), 5,60 (s, 2H), 6,58 (d, 2H), 7,29 (d, 2H).

MS (m/z) / M+1= 289/290

HPLC (pureza uv, λ= 214 nm): 97,61%

Ejemplo I100.2: R_1= ciclohexilo, R_2= metilo, R_3= 4-(N-ciano-N'-(2-dimetilaminoetil)carboximidamido)-fenilo

[5-(4-(N-ciano-N'-(2-dimetilaminoetil)-carboximidamido)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

A una solución de difenilcianocarbonimidato (0,364 mmol, 0,087 mmol) en acetonitrilo (1 ml) a 70°C, se agregó I100.1 (0,347 mmol, 0,1 g) y la mezcla de la reacción se calentó a 80°C durante 15 h. Se agregó 1 eq. de carbonimidato y la mezcla se mantuvo a 80°C durante otras 5 h antes de la evaporación de los volátiles. El residuo se mezcló con etanol (2 ml) y N,N-dimetiletlen diamina (0,34 mmol, 0,038 mg). La mezcla se agitó a temperatura ambiente durante 15 h y se calentó a reflujo durante 5 h. Después de enfriar a temperatura ambiente, el precipitado formado se filtró y se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 2% al 5% de metanol.

Rendimiento= 32%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,16-1,41 (m, 5H), 1,50-1,70 (m, 1H), 1,80-1,91 (m, 4H), 2,35 (s, 6H), 2,50-2,60 (m, 3H), 3,31-3,38 (m, 2H), 3,55 (s, 3H), 6,00-6,10 (b, 1H), 7,30 (d, 2H), 7,52 (d, 2H).

MS (m/z) / M+1 = 427/428

HPLC (pureza uv, λ= 214 nm): 97,23%

Ejemplo I100.3: R_1= ciclohexilo, R_2= metilo, R_3= 4-acetamido-fenilo

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida

A una solución de I100.1 (0,347 mmol, 0,1 g) en presencia de trietilamina (0,361 mmol, 0,051 ml) en tolueno anhidro (3 ml) a 0°C, se agregó anhídrido acético (0,382 mmol, 0,036 ml) y la mezcla de la reacción se agitó a temperatura ambiente durante 20 h y luego se concentró hasta secarse. El residuo se mezcló con una solución saturada de bicarbonato de sodio y luego la mezcla acuosa se extrajo con diclorometano. La capa orgánica se lavó con agua, solución salina, se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con una mezcla de metanol/diclorometano (2/98).

Rendimiento= 22%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,22-1,45 (m, 5H), 1,58-1,68 (m, 1H), 1,80-1,88 (m, 4H), 2,21 (s, 3H), 2,58-2,64 (m, 1H), 3,60 (3H, s), 7,20 (s, 1H), 7,52-7,62 (m, 4H).

MS (m/z) / M+1 = 331:332

HPLC (pureza uv, λ= 214 nm): 95,24%

Ejemplo I100.4: R_1= ciclohexilo, R_2= metilo, R_3= 4-(bis-etilsulfonil-amino)-fenilo

[5-(4-(bis-etilsulfonilamino)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

A una solución de I100.1 (0,347 mmol, 0,1 g) en diclorometano (5 ml) con trietilamina (0,520 mmol, 0,072 ml), se agregó cloruro de clorosulfonilo (0,590 mmol, 0,057 ml) a 0°C y la mezcla se agitó a temperatura ambiente durante 4h30 antes de la evaporación hasta secarse bajo presión reducida. El material crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 5% de metanol.

Rendimiento= 76%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,52 (m, 11H), 1,61-1,68 (m, 1H), 1,80-1,89 (m, 4H), 2,59-2,68 (m, 1H), 3,58-3,64 (m, 7H), 7,40 (d, 2H), 7,70 (d, 2H).

MS (m/z) / M+1= 473/475

HPLC (pureza uv, λ= 214 nm): 98,68%

Ejemplo I100.5: R_1= ciclohexilo, R_2= metilo, R_3= 4-(1-(2-dimetilaminoetil)amino-2-nitro-vinilamino)-fenilo

[5-(4-(1-(2-dimetilaminoetil)amino-2-nitro-vinilamino)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

A una solución de 1,1-bis(metiltio)-2-nitroetileno (1,041 mmol, 0,172 g) en acetonitrilo (1 ml), a 75°C, se agregó I100.1 (0,347 mmol, 0,1 g) y la reacción se calentó a reflujo durante 7 h. La mezcla de la reacción luego se evaporó hasta secarse y el material crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 5% de metanol para dar el intermedio deseado (0,09 g, rendimiento: 64%).

Una mezcla de etilendiamina (0,133 mmol, 0,017 ml) y este intermedio (0,111 mmol, 0,045 g) en etanol (2 ml) se calentó a reflujo durante 3 h. La mezcla se concentró bajo presión reducida para dar un residuo que se purificó mediante cromatografía sobre gel de sílice eluyendo con diclorometano que contenía el 2% de metanol.

Rendimiento= 90%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,23-1,49 (m, 5H), 1,65-1,70 (m, 1H), 1,78-1,88 (m, 4H), 2,45 (s, 6H), 2,57-2,71 (m, 3H), 3,51-3,61 (m, 5H), 6,66 (s, 1H), 7,09 (d, 2H), 7,60 (d, 2H), 10,55-10,62 (b, 1H), 12,28-12,40 (b, 1H).

MS (m/z) / M+1= 446/447

HPLC (pureza uv, λ= 214 nm): 99,34%

Ejemplo I100.6: R_1= ciclohexilo, R_2= metilo, R_3= 4-(1-amino-2-nitro-vinilamino)-fenilo

(E)-N^1-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-2-nitro-eteno-1,1-diamina

El producto del título se preparó mediante el procedimiento descripto en el ejemplo I100.5 usando una solución de amoníaco (2N) en metanol (80 eq) en lugar de etilendiamina.
El producto deseado se aisló mediante cromatografía sobre gel de sílice, eluyendo con un gradiente de diclorometano que contenía del 2% al 4% de metanol.
Rendimiento= 83%
^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,47 (m, 5H), 1,62-1,67 (m, 1H), 1,76-1,87 (m, 4H), 2,60-2,66 (m, 1H), 3,60 (m, 3H), 6,70 (s, 1H), 7,24 (d, 2H), 7,67 (d, 2H).
MS (m/z) / M+1 = 375/376
HPLC (pureza uv, λ= 214 nm): 94,09%

Ejemplo I100.7: R_1= ciclohexilo, R_2= metilo, R_3= 4-(*N*-ciano-*N'*-metil-carboximidamido)-fenilo

[5-(*N*-ciano-*N'*-metil-4-carboximidamido-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

A una solución de difenilcianocarbonimidato (0,364 mmol, 0,087 mmol) en acetonitrilo (1 ml) a 70°C, se agregó I100.1 (0,347

mmol, 0,1 g) y la mezcla de la reacción se calentó a 80°C durante 15 h. Se agregó un equivalente de difenilcianocarbonimidato y la mezcla se agitó durante 5 h. La mezcla se concentró bajo presión reducida para dar el intermedio que se usó sin nueva purificación. El intermedio (0,416 mmol, 0,300 g) en una solución (2N) de metilamina en MeOH (32,890 mmol, 16,64 ml) se refluyó durante 8 h, luego se dejó en reposo a temperatura ambiente durante 2 días. La mezcla se evaporó hasta secarse y el residuo se purificó por cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 4% de metanol para dar el producto deseado.

Rendimiento= 29%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,45 (m, 5H), 1,62-1,67 (m, 1H), 1,76-1.87 (m, 4H), 2,57-2,67 (m, 1H), 2,90 (d, 3H), 3,60 (m, 3H), 4,90-5,01 (b, 1H), 7,17-7,28 (m, 3H), 7,69 (d, 2H).

MS (m/z) / M+1= 370/371

HPLC (pureza uv, λ= 214 nm): 99,99%

Ejemplo I100.8: R_1= ciclohexilo, R_2= metilo, R_3= 4-(N-ciano-N'-amino-carboximidamido)-fenilo

[5-(4-(N-ciano-N'-amino-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina

El producto del título se preparó mediante el procedimiento descripto en el ejemplo I100.7 usando el mismo intermedio (0,416 mmol, 0,300 g) y una solución (2N) de amoníaco en metanol (32,89 mmol, 16,64 ml). El producto deseado se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 7% de metanol.

Rendimiento= 67%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,46 (m, 5H), 1,60-1,66 (m, 1H), 1,78-1,88 (m, 4H), 2,55-2,65 (m, 1H), 3,58 (m, 3H), 6,10 (s, 2H), 7,42 (d, 2H), 7,55 (d, 2H), 8,71 (s, 1H).

MS (m/z) / M+1 = 356/357

HPLC (pureza uv, λ= 214 nm): 97,39%

Ejemplo I100.9: R_1= ciclohexilo, R_2= metilo, R_3= 4-etilsulfonilamino-fenilo

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-amida del ácido etanosulfónico

Se agregó cloruro de etilsulfonilo (0,416 mmol, 0,040 ml) a una solución de I100.1 (0,347 mmol, 0,10 g) en diclorometano a 0°C. La mezcla se agitó durante 12 h a temperatura ambiente, luego se basificó con una solución saturada de bicarbonato de sodio. La capa orgánica se recogió y se concentró bajo presión

reducida. El material crudo reaccionó con 1,1-bis(metiltio)-2-nitroetileno (2,690 mmol, 0,445 g, 10 eq) a reflujo en acetonitrilo (5 ml) durante 24 h. El solvente se destiló luego bajo presión reducida y el residuo se purificó mediante cromatografía sobre gel de sílice con diclorometano que contenía un gradiente del 0% al 10% de metanol.

Rendimiento= 15%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,24-1,44 (m, 8H), 1,62-1,68 (m, 1H), 1,78-1,87 (m, 4H), 2,59-2,65 (m, 1H), 3,14-3,19 (q, 2H), 3,60 (s, 3H), 6,44 (s, 2H), 7,23 (dd, 2H), 7,61 (dd, 2H).

MS (m/z) / M+1= 381/383

HPLC (pureza uv, λ= 214 nm): 99,22%

Ejemplo I100.10: R_1= ciclohexilo, R_2= metilo, R_3= 4-Ureido-fenilo

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-urea

A una solución de I100.1 (0,348 mmol, 0,100 g) en TJF (1 ml), se agregó isocianato de trimetilsililo (0,416 mmol, 0,488 ml) y la mezcla se agitó a temperatura ambiente durante 10h y se agregó agua. La capa orgánica se extrajo con acetato de etilo, se lavó con agua, solución salina, se secó sobre $MgSO_4$, se filtró y luego se evaporó hasta secarse. El producto crudo se

purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de diclorometano que contenía del 0% al 4% de metanol.

Rendimiento= 13%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,24-1,39 (m, 5H), 1,53-1,57 (m, 1H), 1,69-1,80 (m, 4H), 2,57-2,65 (m, 1H), 3,47 (s, 3H), 5,92 (s, 2H), 7,50 (s, 4H), 8,79 (s, 1H).

MS (m/z) / M+1= 332/333

HPLC (pureza uv, λ= 214 nm): 92,50%

Ejemplo I100.11: R_1= cicloheilo, R_2= metilo, R_3= 4-[3-(2-dimetilamino-etil)-ureido]-fenilo

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea

A una solución de I100.1 (0,347 mmol, 0,100 g) con trietilamina (1,041 mmol, 0,145 ml) en diclorometano anhidro (5 ml), se agregó una solución de fosgeno (20% en tolueno) (1,024 mmol, 0,487 ml) a 0°C. La mezcla se agitó a 0°C durante 10 minutos, luego se dejó elevar la temperatura durante 1 h y se agregó N,N-dimetil-etilen daimina (0,694 mmol, 0,076 ml). Después de 20 h de agitación a temperatura ambiente, la mezcla se basificó con una solución saturada de bicarbonato de sodio, luego se extrajo con diclorometano. La fase orgánica se lavó

con agua, solución salina, se secó sobre $MgSO_4$, se filtró y se evaporó hasta secarse. El residuo se cromatografió sobre gel de sílice eluyendo con una mezcla de diclorometano/metanol (95/5) para lograr el producto del título.

Rendimiento= 11%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,50 (m, 5H), 1,70-1,75 (m, 1H), 1,78-1,90 (m, 4H), 2,33 (s, 6H), 2,58-2,68 (m, 3H), 3,30-3,40 (b, 2H), 3,60 (s, 3H), 5,37-5,47 (b, 1H), 7,40 (d, 2H), 7,55 (d, 2H).

MS (m/z) / M+1 = 403/404

HPLC (pureza uv, λ= 214 nm): 99,99%

Ejemplo I101: I101: R_1= ciclohexilo, R_2= metilo, R_3= 3-cloro-4-sulfamoil-fenilo

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencensulfonamida

El compuesto del título se preparó mediante el procedimiento descripto en el ejemplo I15 (protocolo D) usando los intermedios y reactivos apropiados.

El producto deseado se aisló por cromatografía sobre gel de sílice, eluyendo con un gradiente de ciclohexano que contenía del 0% al 30% de acetato de etilo.

Rendimiento: 23%

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,21-1,49 (m, 5H), 1,60-1,69 (m, 1H), 1,79-1,87 (m, 4H), 2,59-2,69 (m, 1H), 3,60 (m, 3H), 5,10 (s, 2H), 7,58 (d, 1H), 7,80 (s, 1H), 8,10 (d, 1H).

MS (m/z) / M+1 = 388/389

HPLC (pureza uv, λ= 214 nm): 98,32%

Ejemplo I102: R_1= ciclohexilo, R_2= metilo, R_3= 3-cloro-4-metoxicarbonil-fenilo

Metil éster del ácido 2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico

I102 se preparó mediante el procedimiento descripto en el ejemplo I15 (protocolo D) usando los intermedios y reactivos apropiados. El producto deseado se aisló por cromatografía sobre gel de sílice eluyendo con un gradiente de ciclohexaneo que contenía del 0% al 7% de acetato de etilo. (rendimiento: 12%)

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,21-1,48 (m, 5H), 1,60-1,67 (m, 1H), 1,78-1,87 (m, 4H), 2,58-2,66 (m, 1H), 3,60 (s, 3H), 4,93 (s, 3H), 7,55 (d, 1H), 7,71 (s, 1H), 7,86 (d, 1H).

Ejemplo 102.1: R_1= ciclohexilo, R_2= metilo, R_3= 3-cloro-4-benzamida

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

A una solución de I102 (0,391 mmol, 0,147 g) en una mezcla de THF/MeOH (2 ml) (1/1), se agregó hidróxido de litio (0,430 mmol, 0,010 g) y la mezcla de la reacción se dejó agitar durante 15h a temperatura ambiente. Se agregó hidróxido de litio (0,430 mmol, 0,010 g) y la reacción se agitó durante 24 h antes de la evaporación hasta secarse. El material se acidificó con una solución de HCl (1N), se agitó a temperatura ambiente durante 3h y la mezcla se concentró hasta secarse.

Se agregó tolueno (5 ml) al residuo (0,273 mmol, 0,120 g) y luego se agregó cloruro de tionilo (0,820 mmol, 0,598 ml) y la mezcla se calentó a reflujo toda la noche hasta la destilación de los volátiles bajo presión reducida. El residuo ser vertió en THF (5 ml) y se enfrió a 0°C luego se agregó una solución de amoníaco concentrado (6,833 mmol, 0,448 ml). Se dejó que la reacción se agitara a tempratura ambiente durante 3 h y luego el solvente se destiló. El residuo se purificó mediante cromatografía sobre gel de sílice, eluyendo con dicorometano que contenía del 0% al 1% de metanol.

Rendimiento: 63% (en total)

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,48 (m, 5H), 1,62-1,69 (m, 1H), 1,79-1,88 (b, 4H), 2,58-2,67 (m, 1H), 3,60 (m, 3H), 5,86-

5,93 (b, 1H), 6,38-6,48 (b, 1H), 7,57 (d, 1H), 7,70 (s, 1H), 7,87 (d, 1H).

MS (m/z) / M+1= 351/353

HPLC (pureza uv, λ= 214 nm): 96,60%

Ejemplo I103: R_1= ciclohexilo, R_2= metilo, R_3= 4-cloro-3-benzamida

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida

El compuesto del título se preparó mediante el procedimiento descripto en el ejemplo I102.1 usando los intermedios y reactivos apropiados (protocolo D).

^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 1,20-1,42 (m, 5H), 1,60-1,69 (m, 1H), 1,77-1,89 (b, 4H), 2,55-2,65 (m, 1H), 3,60 (m, 3H), 5,89-6,00 (b, 1H), 6,30-6,40 (b, 1H), 7,46 (d, 1H), 7,68 (d, 1H), 8,00 (s, 1H).

MS (m/z) / M+1 = 351/353

HPLC (pureza uv, λ= 214 nm): 98,70%

PROTOCOLO E: Intermedio 8

R_1= ciclohexilo, R_2= metilo, R_3= 4-metoxicarbonil-fenilo

1-(4-metoxicarbonil-benzoil)-2-metil-4-ciclohexil-tiosemicarbazida

A una solución agitada de 5a (2,517 mmol, 0,456 g) en piridina (6 ml), se agregó metil-4-cloro carbonil benzoato (2,517 mmol, 0,500 g). La mezcla se agitó durante 24 h a RT, y luego la piridina se destiló bajo presión reducida con diclorometano. La capa orgánica se lavó con agua, solución salina, se secó sobre $MgSO_4$ y se concentró hasta secarse para lograr 1,10 g del producto.

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,15-1,25 (m, 5H), 1,51-1,61 (m, 1H), 1,61-1,71 (m, 2H), 1,71-1,87 (m, 2H), 3,28 (s, 3H), 3,9 (s, 3H), 4,10-4,21 (m, 1H), 8,00-8,10 (m, 4H), 8,59 (d, 1H), 10,79 (s, 1H).

EJEMPLO I: PROTOCOLO E

Ejemplo I104: R_1= ciclohexilo, R_2= metilo, R_3= 4-metoxicarbonil-fenilo

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzoico

Una mezcla agitada del intermedio 8 precedente (2,517 mmol, 1,10 g) y metanol (50 ml) se calentó hasta que se obtuvo una solución homogénea, luego se agregó óxido de mercurio (10,068 mmol, 2,18 g). Después de 18h a reflujo, se agregaron otros 3 equivalentes de HgO y la reacción se mantuvo a reflujo durante otras 6 h, luego se dejó enfriar a la temperatura ambiente. La

reacción filtró a través de un tampón de Celita y el filtrado se evaporó bajo presión reducida. El material crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con ciclohexano que contenía del 1% al 20% de acetato de etilo.

Rendimiento= 44%

^{1}H-NMR (400MHz, DMSO) δ ppm: 1,1-1,4 (m, 5H), 1,53-1,61 (m, 1H), 1,69-1,80 (m, 1H), 3,30 (s, 3H), 3,40-3,48 (m, 1H), 3,88 (s, 3H), 3,85 (d, 2H), 7,96 (d, 2H), 8,08 (d, 2H).

MS (m/z) / M+1 =316/318

Ejemplo I104.1: R_1= ciclohexilo, R_2= metilo, R_3= 4-benzamida

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzamida

El compuesto del título se preparó mediante un procedimiento descripto en el ejemplo I37.3. El producto deseado se aisló mediante cromatografía sobre gel de sílice eluyendo con diclorometano que contenía del 1% al 2% de metanol.

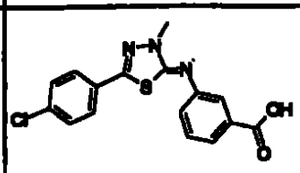
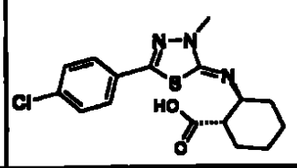
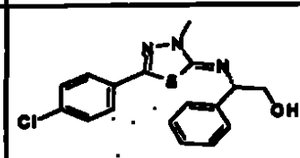
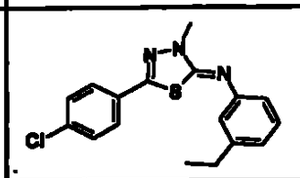
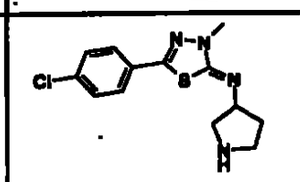
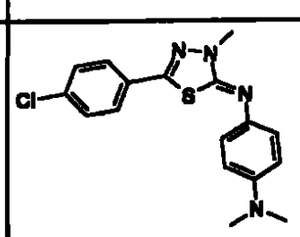
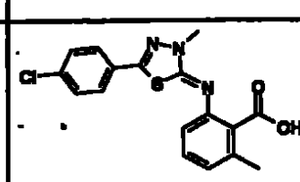
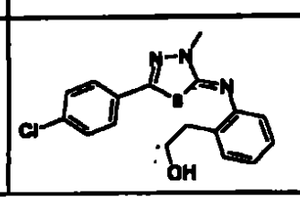
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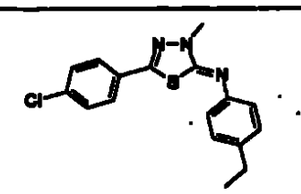
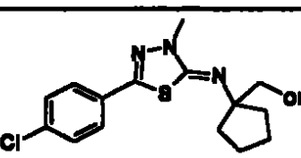
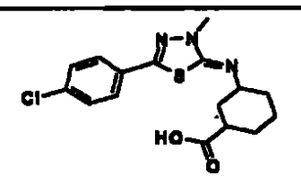
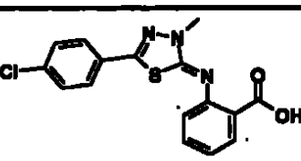
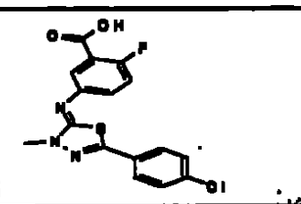
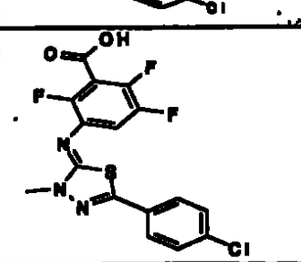
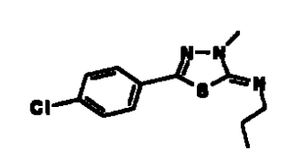
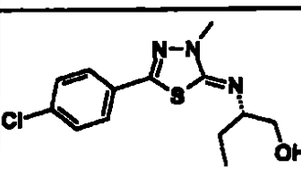
^{1}H-NMR (400MHz, DMSO) δ ppm: 1,17-1,40 (m, 5H), 1,58-1,64 (m, 1H), 1,70-1,80 (m, 4H), 3,30 (s, 3H), 3,41-3,51 (m, 1H), 7,50-7,55 (b, 1H), 7,80 (d, 2H), 8,00 (d, 2H), 8,10-8,18 (b, 1H).

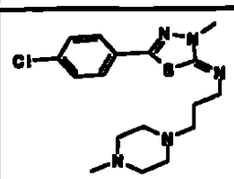
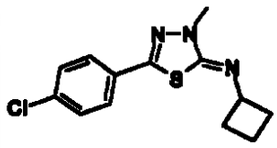
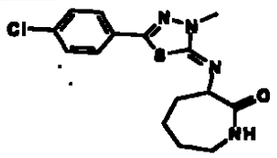
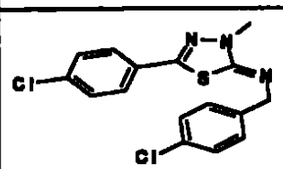
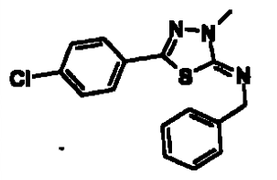
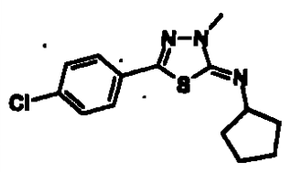
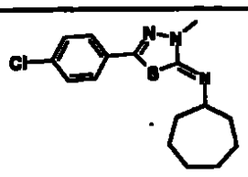
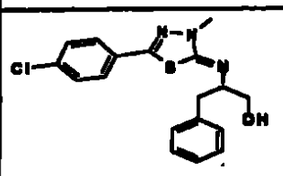
MS (m/z) / M+1 =301/302

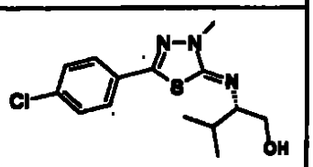
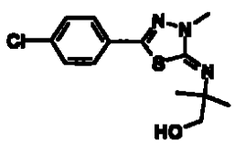
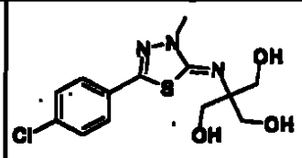
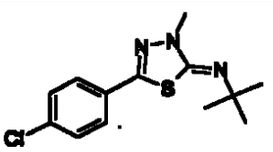
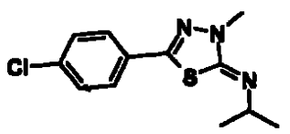
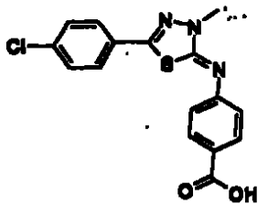
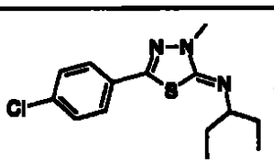
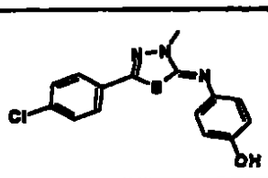
HPLC (pureza uv, λ= 214 nm) = 99,9%

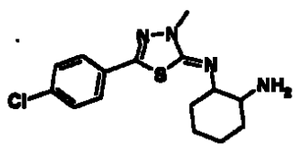
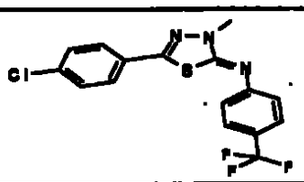
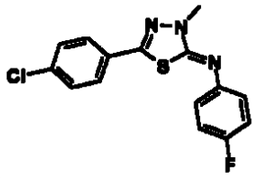
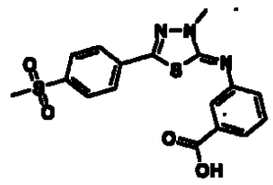
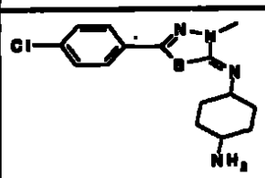
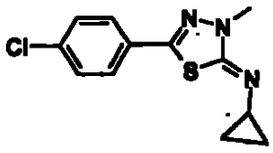
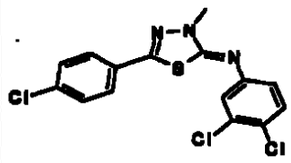
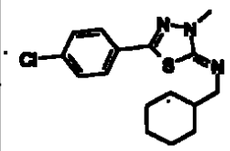
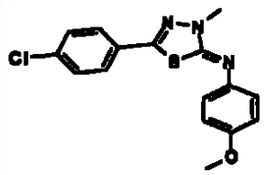
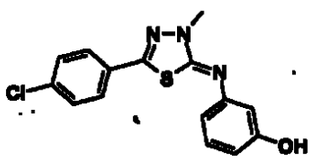
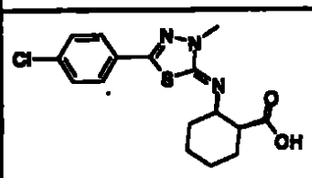
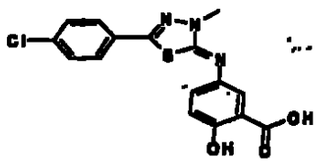
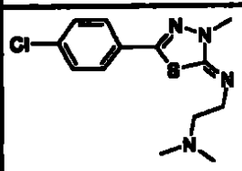
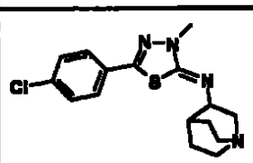
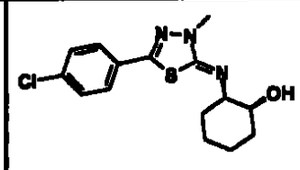
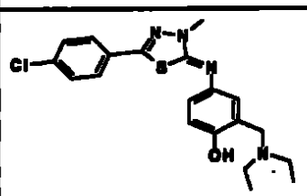
Los compuestos de la fórmula (I) revelados en los ejemplos se resumen en la siguiente tabla:

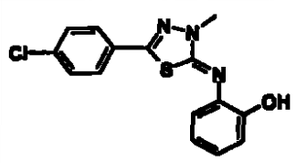
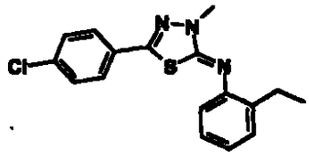
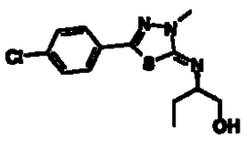
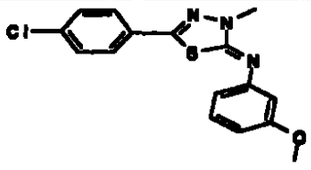
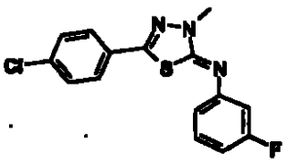
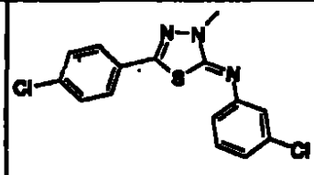
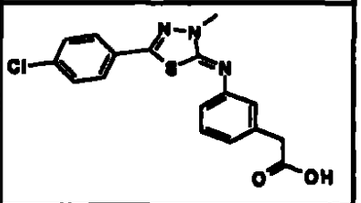
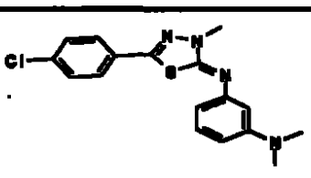
Ejemplo	Estructura
I1	
I1,1	
I1,2	
I1,3	
I1,4	
I1,5	
I1,6	
I1,7	

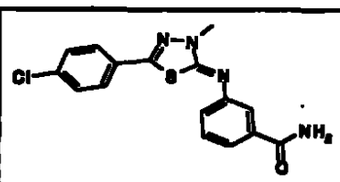
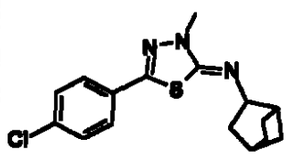
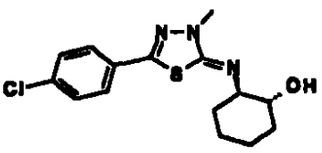
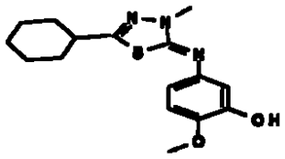
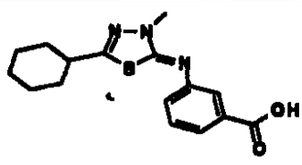
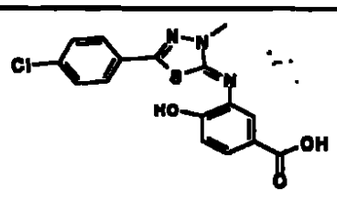
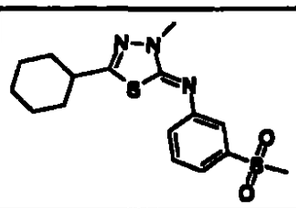
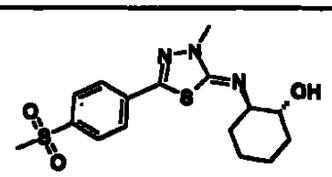
Ejemplo	Estructura
I1,8	
I1,9	
I1,10	
I2	
I2,1	
I2,2	
I3	
I3,1	

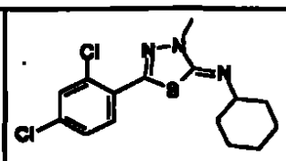
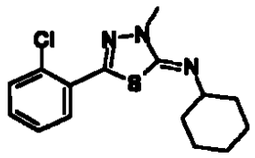
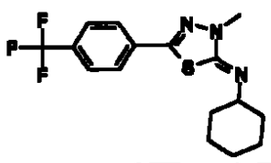
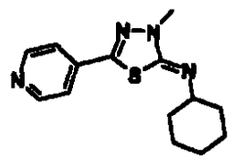
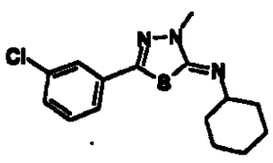
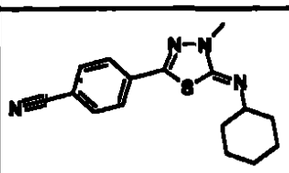
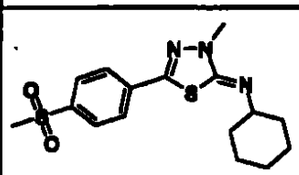
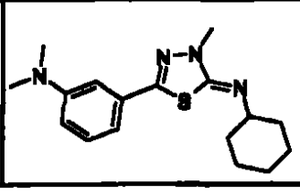
Ejemplo	Estructura
I3,2	
I3,3	
I3,4	
I3,5	
I3,6	
I3,7	
I3,8	
I3,9	

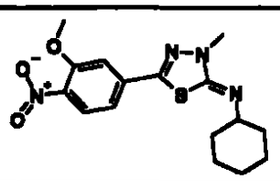
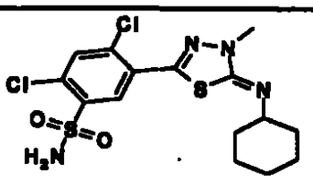
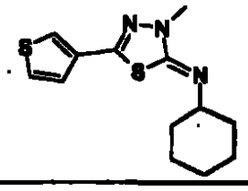
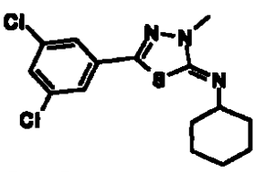
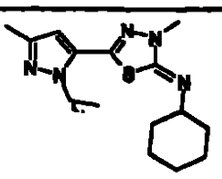
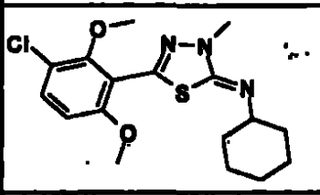
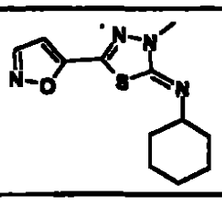
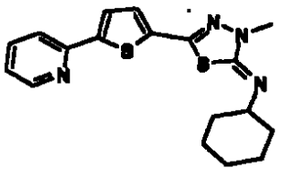
Ejemplo	Estructura
I3,10	
I3,11	
I3,12	
I3,13	
I3,14	
I3,15	
I3,16	
I3,17	

Ejemplo	Estructura	Ejemplo	Estructura
I3,18		I3,26	
I3,19		I4	
I3,20		I4,1	
I3,21		I4,2	
I3,22		I5	
I3,23		I6	
I3,24		I6,1	
I3,25		I6,2	

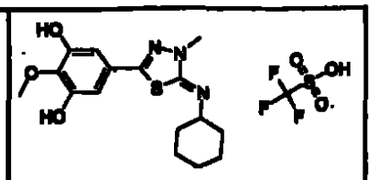
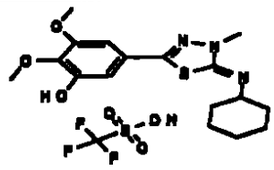
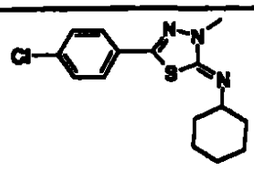
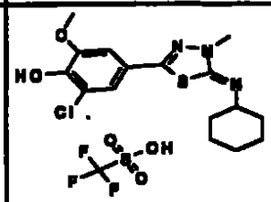
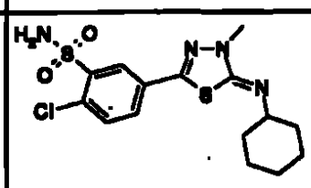
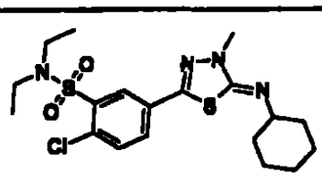
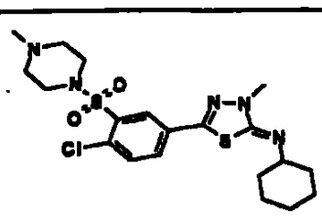
I6,3	
I6,4	
I6,5	
I6,6	
I6,7	
I6,8	
I6,9	
I6,10	

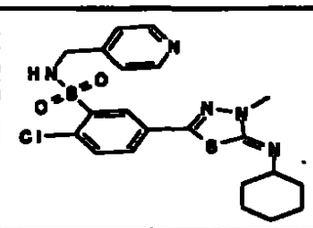
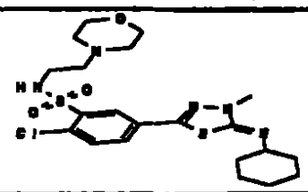
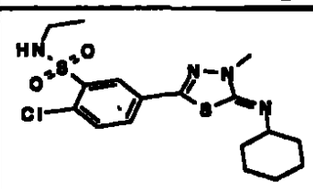
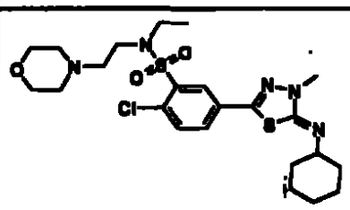
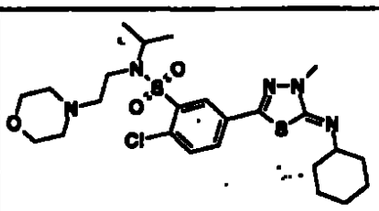
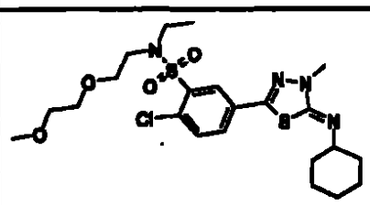
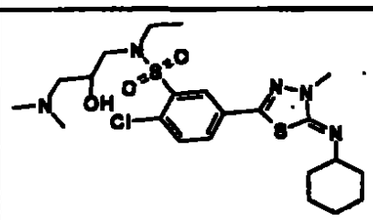
I6,11	
I7	
I8	
I8,1	
I8,2	
I8,3	
I8,4	
I9	

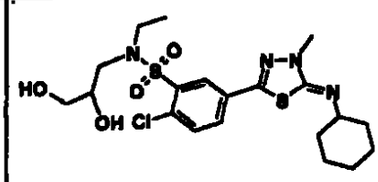
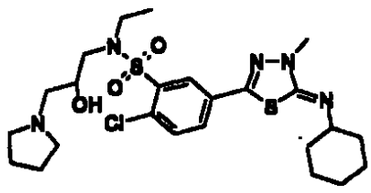
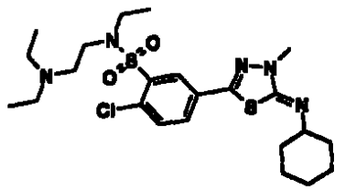
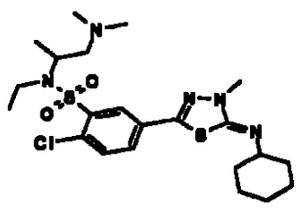
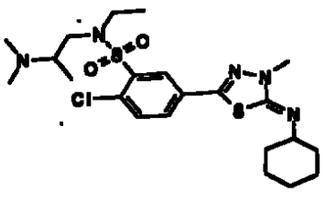
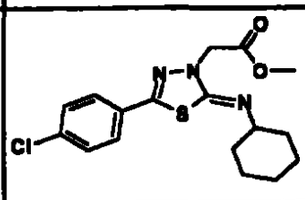
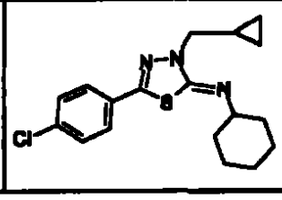
I10	
I10,1	
I11	
I12	
I13	
I14	
I15	
I15,1	

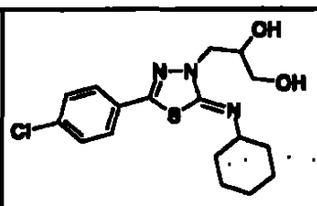
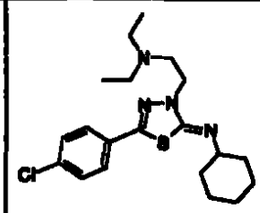
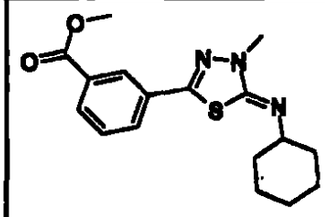
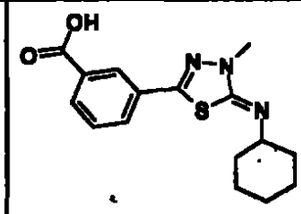
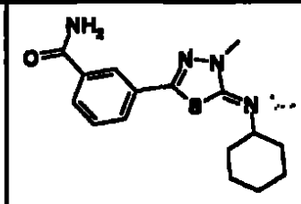
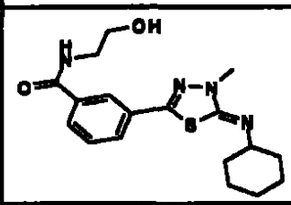
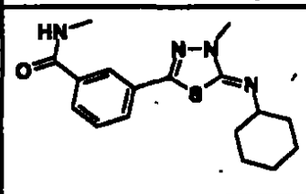
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I16	
I17	
I17,1	
I17,2	
I18	
I18,1	
I18,2	

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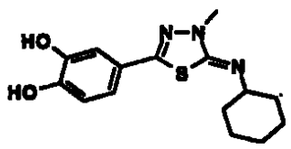
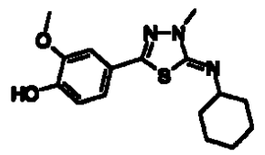
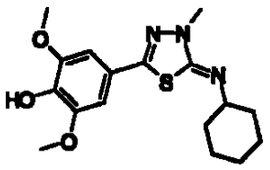
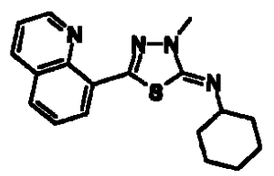
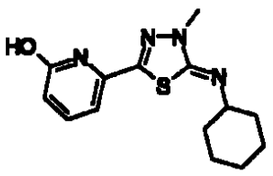
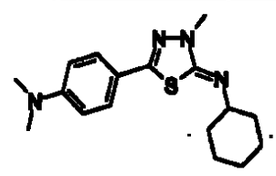
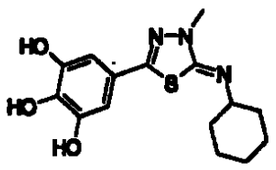
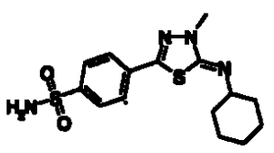
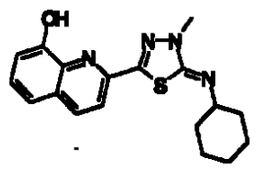
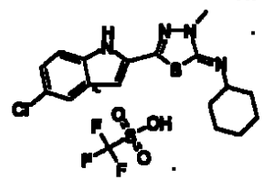
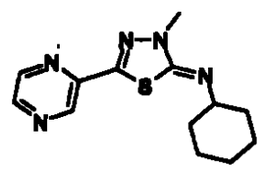
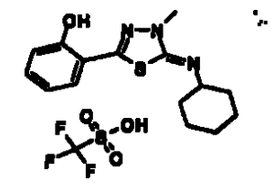
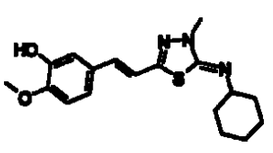
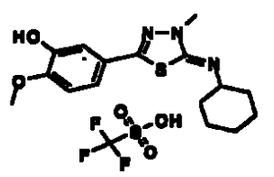
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I19	
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I19,2	

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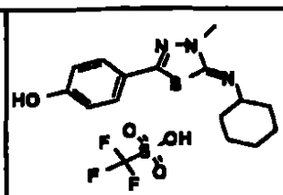
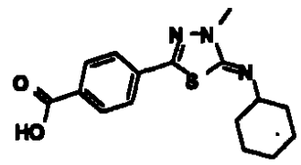
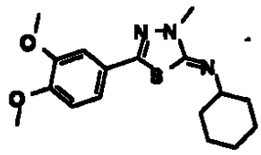
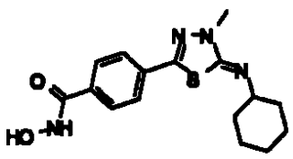
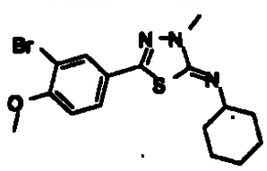
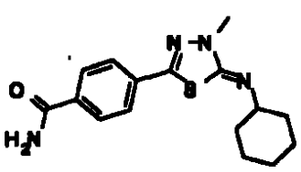
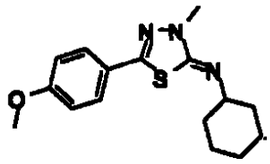
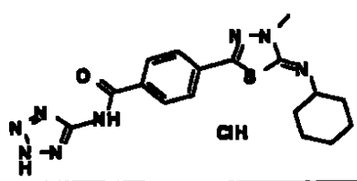
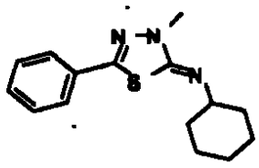
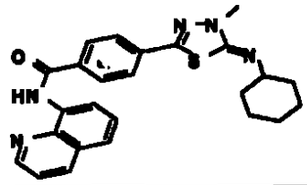
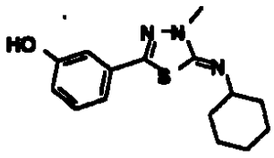
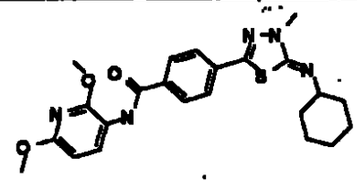
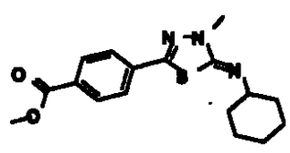
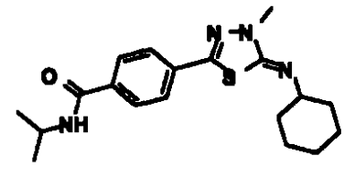
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I20	
I20,1	

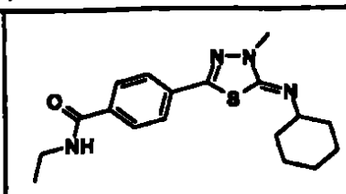
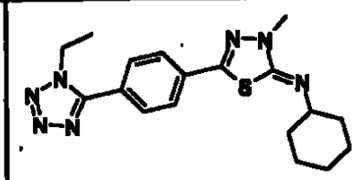
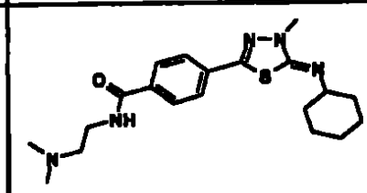
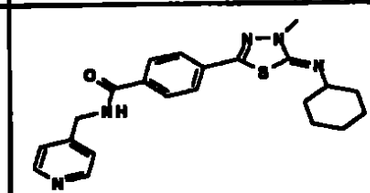
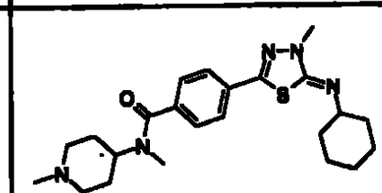
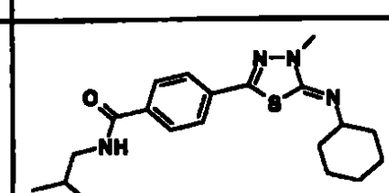
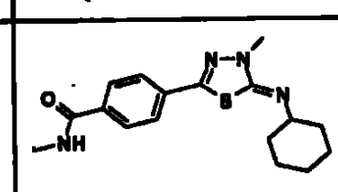
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I21,4	

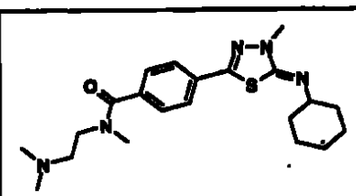
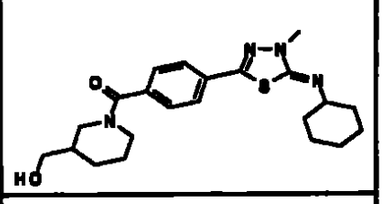
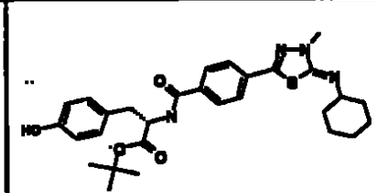
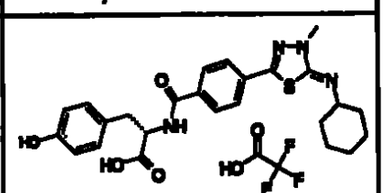
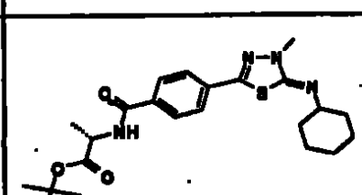
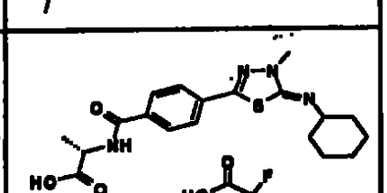
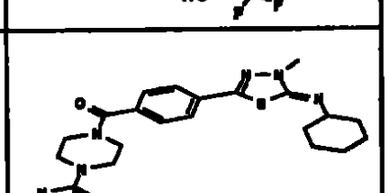
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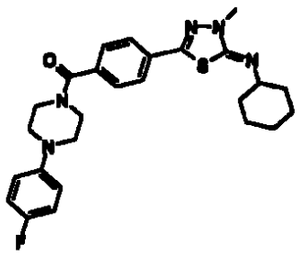
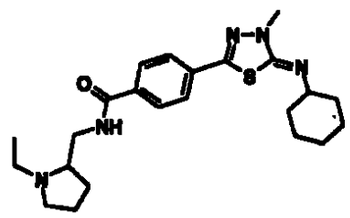
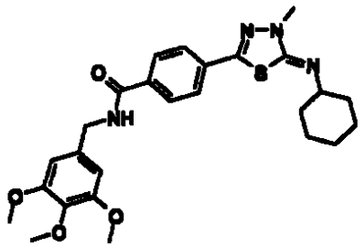
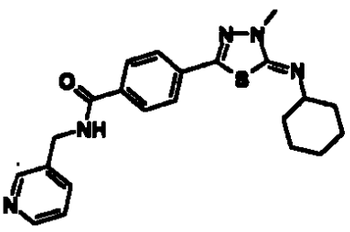
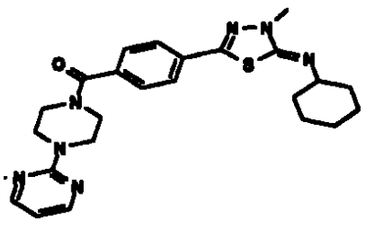
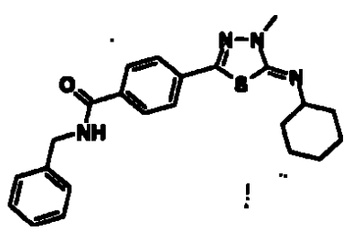
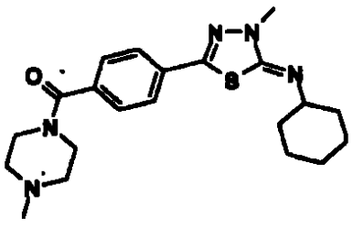
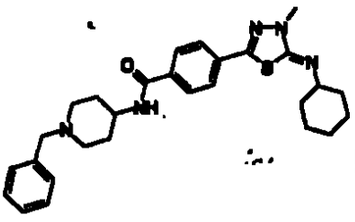
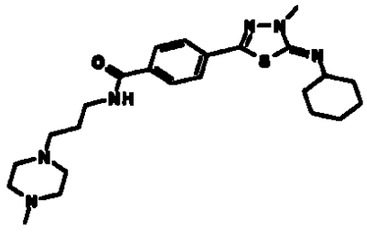
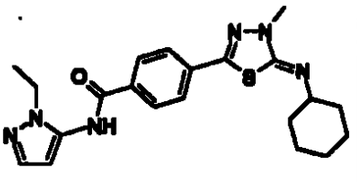
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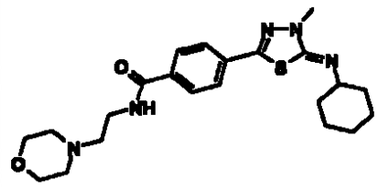
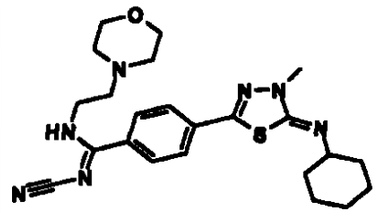
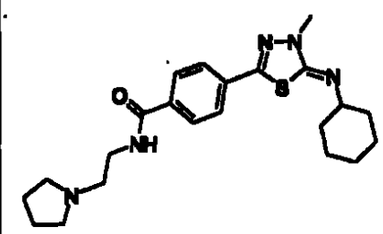
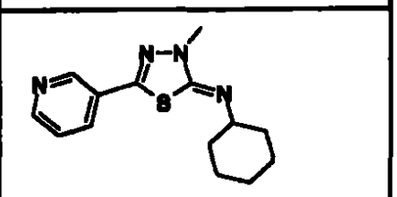
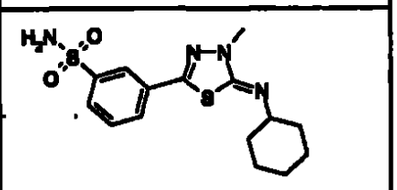
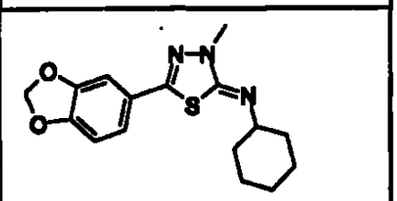
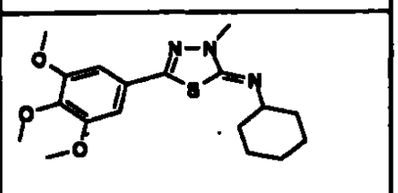
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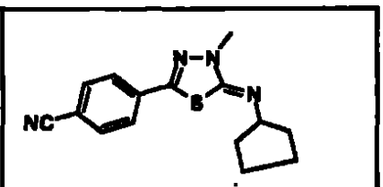
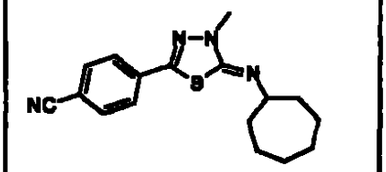
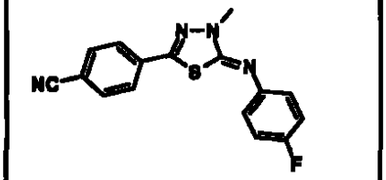
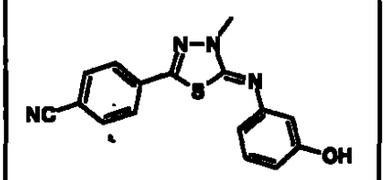
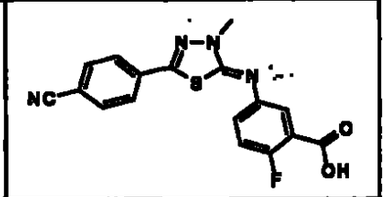
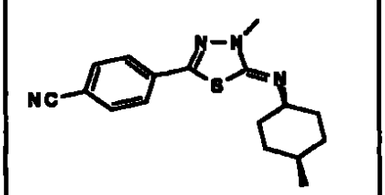
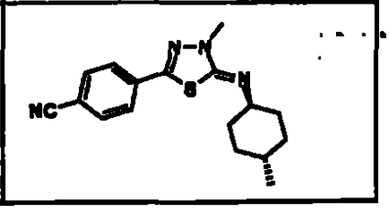
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I37,13	

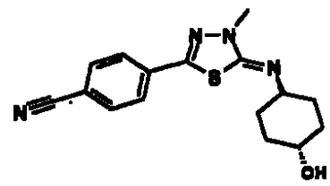
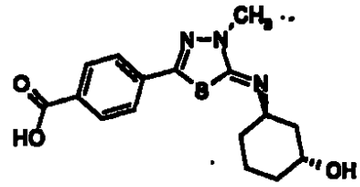
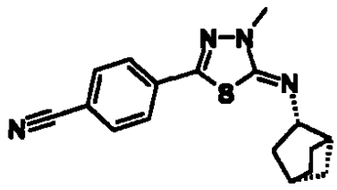
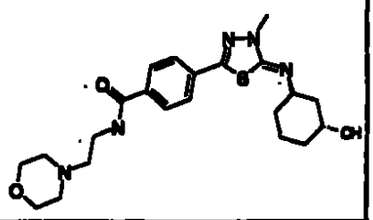
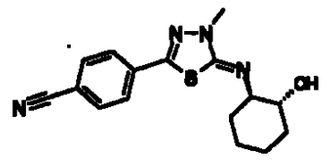
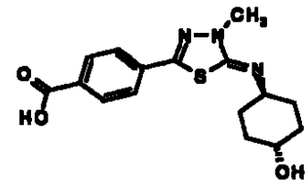
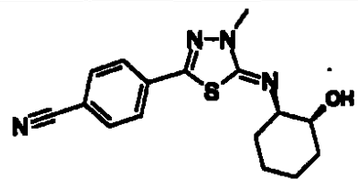
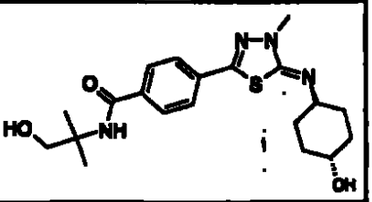
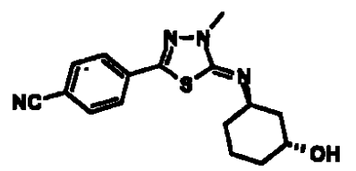
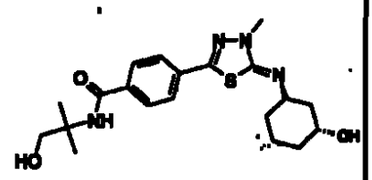
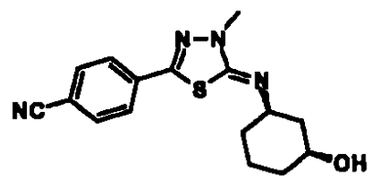
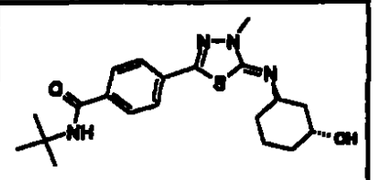
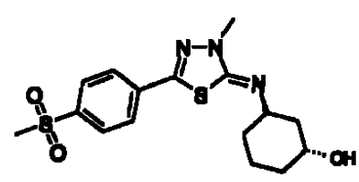
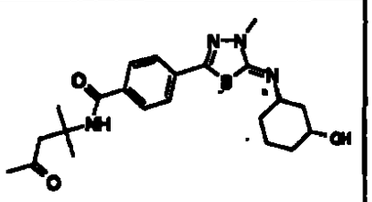
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I37,15-a	
I37,16	
I37,16-a	
I37,17	

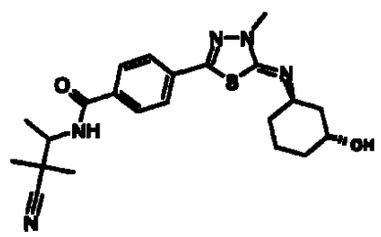
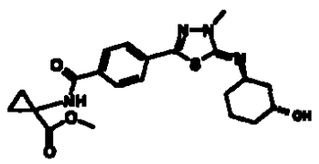
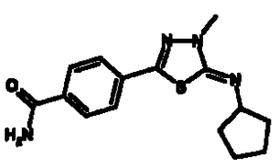
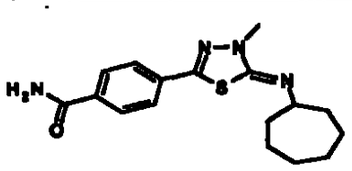
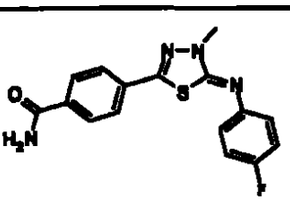
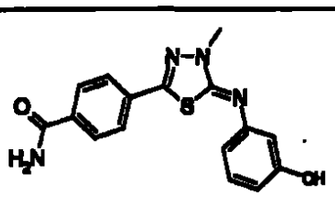
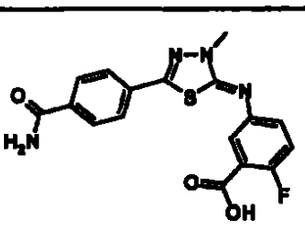
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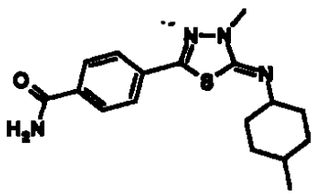
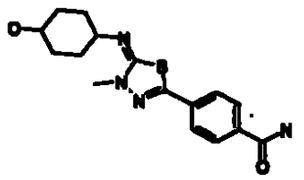
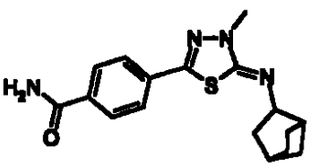
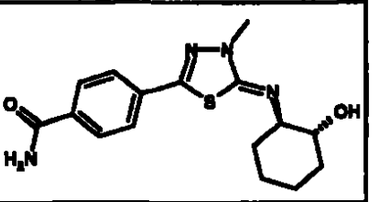
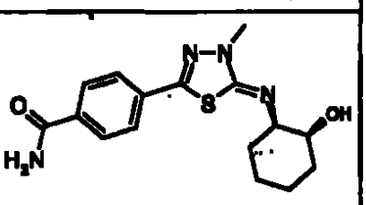
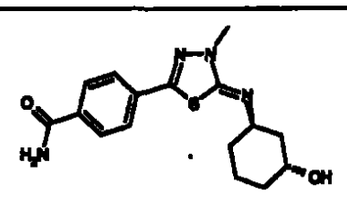
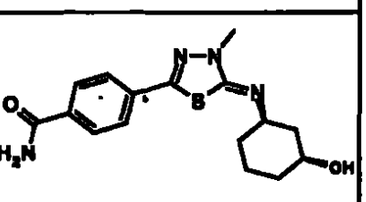
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I37,20		I37,25	
I37,21		I37,26	
I37,22		I37,27	

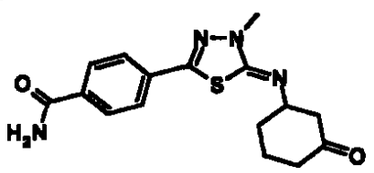
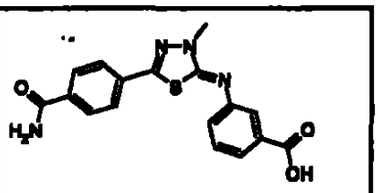
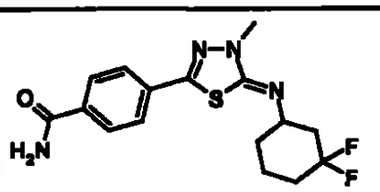
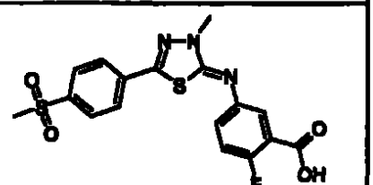
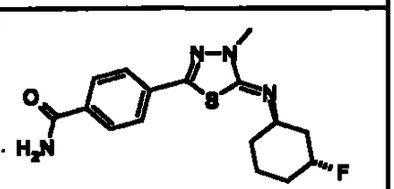
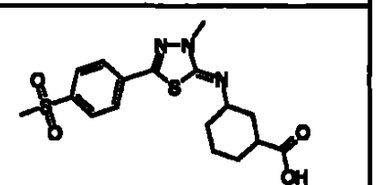
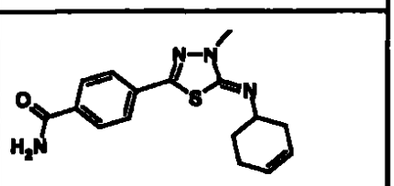
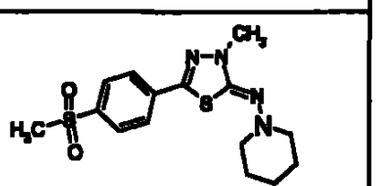
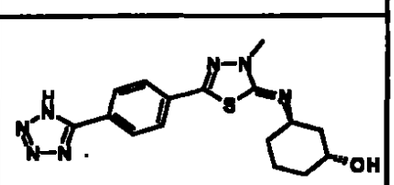
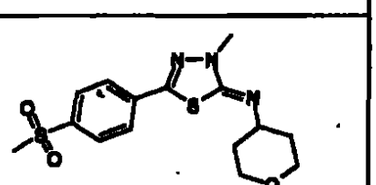
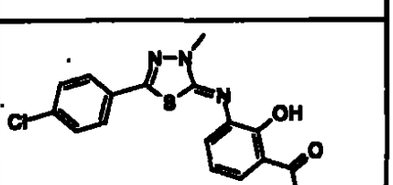
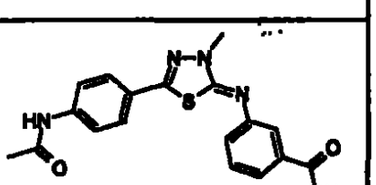
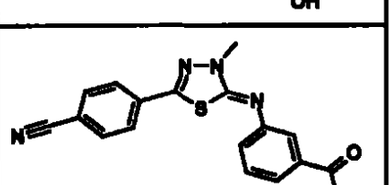
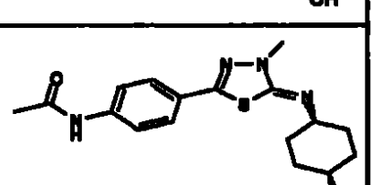
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I38	
I39	
I40	
I41	

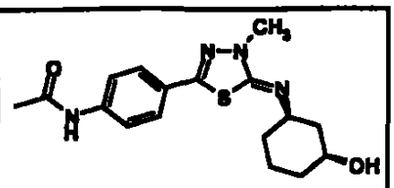
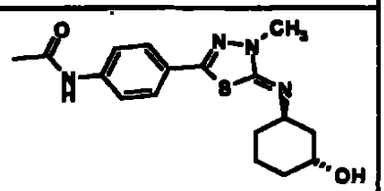
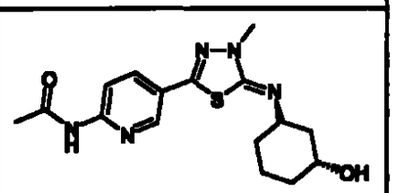
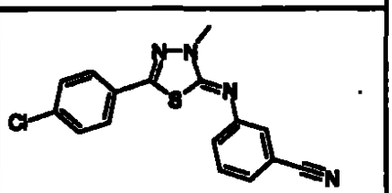
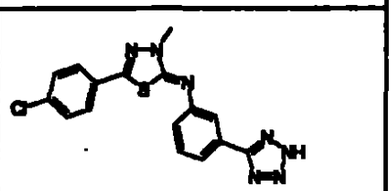
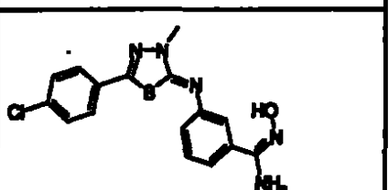
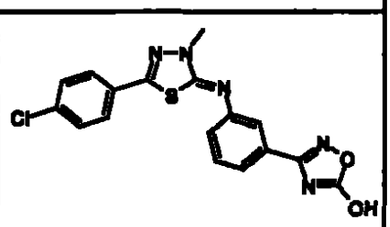
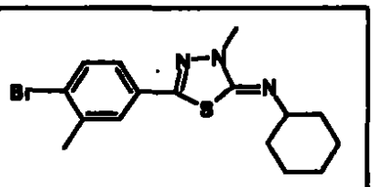
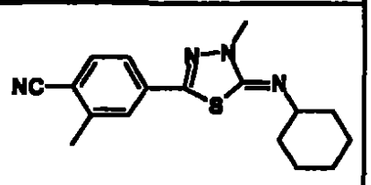
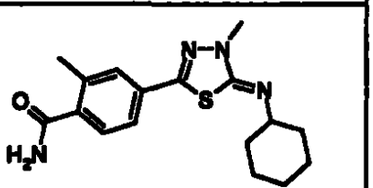
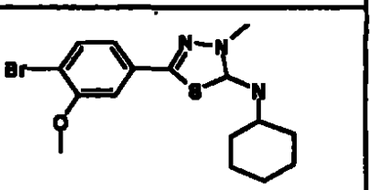
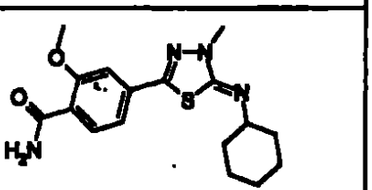
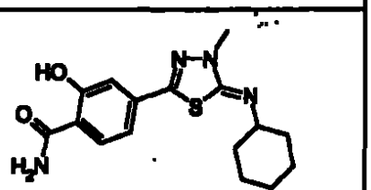
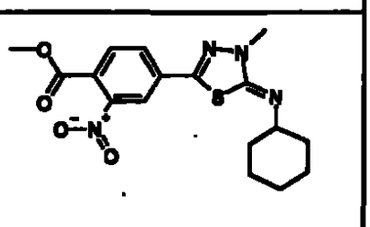
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I45	
I46	
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I47-b	

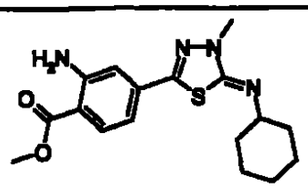
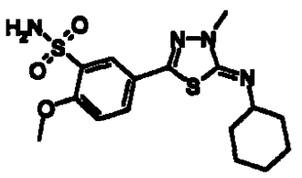
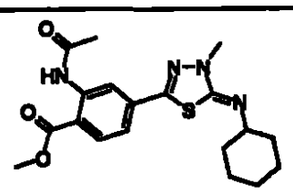
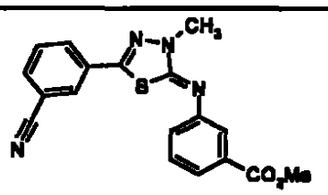
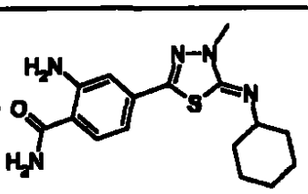
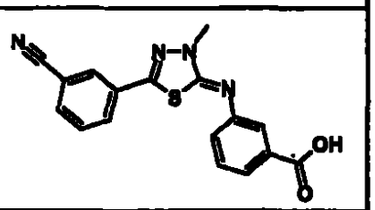
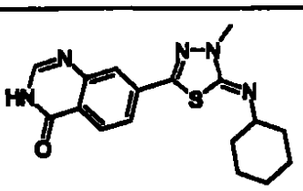
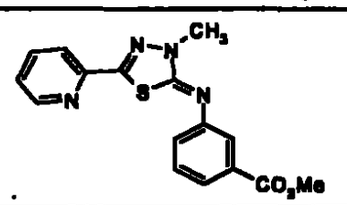
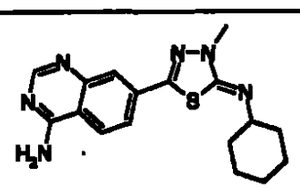
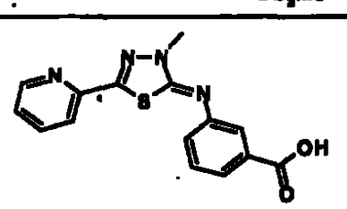
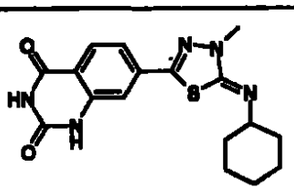
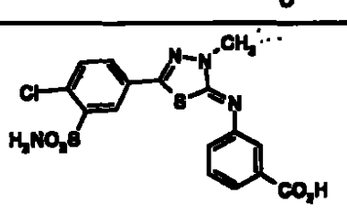
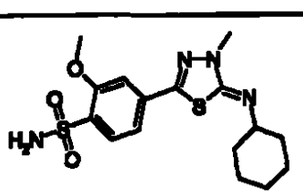
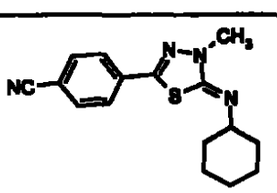
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I53		I60	

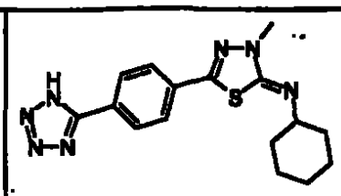
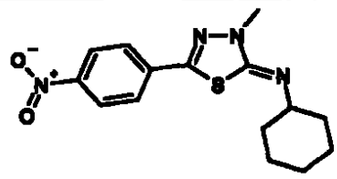
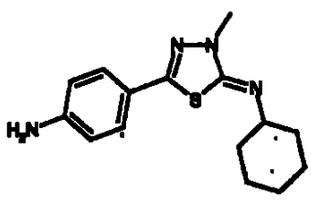
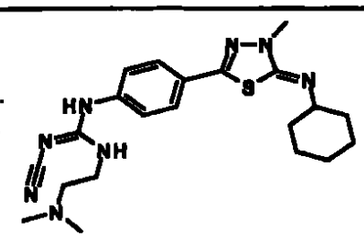
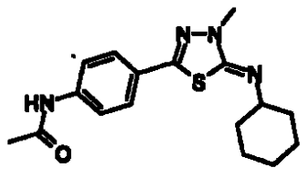
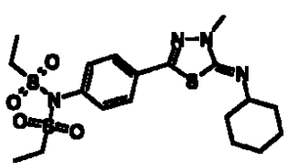
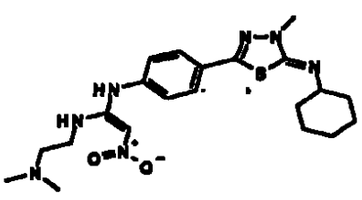
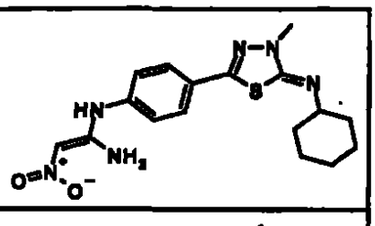
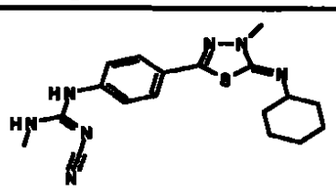
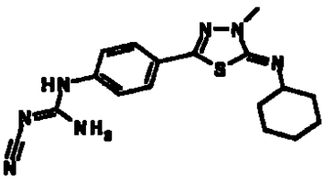
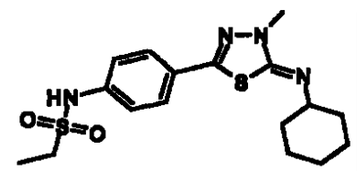
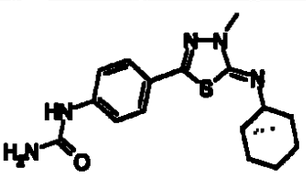
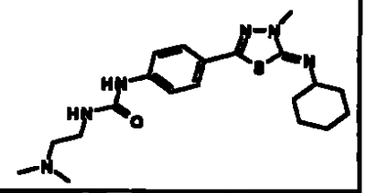
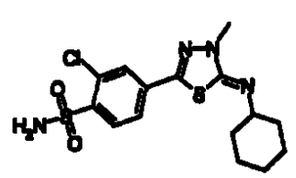
I61	
I62	
I63	
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I67	

I68	
I69	
I70	
I71	
I72	
I73	
I74	

I74,1		I80,1	
I75		I81	
I76		I82	
I77		I83	
I78		I84	
I79		I85	
I80		I86	

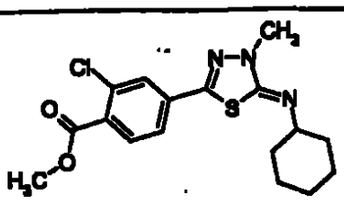
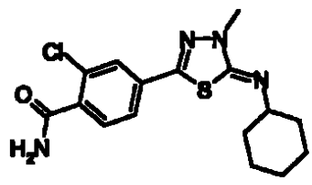
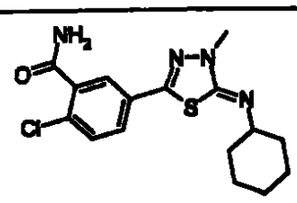
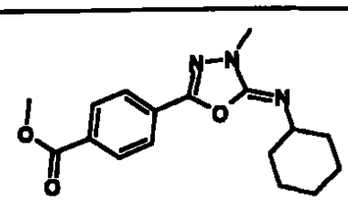
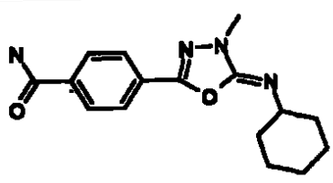
I87	
I88	
I89	
I90	
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I90,2	
I90,3	
I91	
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I91,2	
I92	
I92,1	
I92,2	
I93	

I93,1		I95	
I93,2		I96	
I93,3		I96,1	
I93,4		I97	
I93,5		I97,1	
I93,6		I98	
I94		I99	

I99,1	
I100	
I100,1	
I100,2	
I100,3	
I100,4	
I100,5	
I100,6	
I100,7	
I100,8	
I100,9	
I100,10	
I100,11	
I101	

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I102	
I102,1	
I103	
I104	
I104,1	

Resultados Biológicos

Inhibición in vitro de la fosfodiesterasa 7 y de otras fosfodiesterasas

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La capacidad de los compuestos de la invención de inhibir fosfodiesterasas nucleótidas cíclicas se evaluó midiendo sus IC_{50} (la concentración necesaria para inhibir la actividad enzimática por el 50%).

PDE3A3, PDE4D3, PDE7A1 se clonaron y expresaron en células de insectos Sf21 uaindo el sistema de expresión de baculovirus. La fuente de PDE103 y de PDE503 eran cultivos de células humanas . (respectivamente monocitos humanos TPH1 y adenocarcinoma de mamas caucásico humano MCF7). Los diversos tipos de fosfodiesterasas se obtuvieron parcialmente purificadas sobre una columna de intercambio de aniones (Mono Q) de acuerdo con una adaptación de un método de Lavan B.E., Lakey T., Houslay M.D. Biochemical Pharmacology, 1989, 38 (22), 4123-4136.

La medición de la actividad enzimática para los diversos tipos de PDE se hizo de acuerdo con la adaptación de un método de W.J. Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92, ed. G. Brooker et al. Raven Press, NY.

El sustrato usado fue cGMP para PDE1 y PDE5 y cAMP para PDE 3, PDE 4 y PDE 7. La concentración del sustrato fue 0.2 µM para PDE 1, PDE 3 y PDE 5, 0,25 µM para PDE 4 y 50 nM para PDE 7.

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La reacción enzimática se detuvo después de 1 hora para PDE 1, PDE 3 y PDE 5 y 10 minutos para PDE 4 y PDE 7.

Para determinar sus IC_{50}, los compuestos de la invención se ensayaron en 8 concentraciones en la gama de 0,03 nM a 100 µM para PDE 4 y PDE 7 y en 6 concentraciones en la gama de 0,1 µM a 30 µM para PDE 1, 3 y 5.

Las IC_{50} (µM) se determinaron para algunos de los compuestos de la invención, y los resultados se resumen en la siguiente tabla:

Compuestos	IC_{50} (PDE7)	Compuestos	IC_{50} (PDE7)
I1	0,15	I27	0,46
I2,1	0,13	I28	0,23
I3,25	1,20	I29	0,30
I4	0,15	I30	0,14
I7	1,05	I31	0,23
I8	0,45	I32	0,23
I9	0,28	I33	0,24
I10,1	1,30	I34	0,63
I11	0,98	I35	0,58
I12	0,29	I36	0,29
I13	0,70	I37	0,23

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y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_4-C_{10},

cicloalquilo,

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cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es $X_2-R'_3$ en donde:
  - X_2 es un solo enlace o,

    un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

    1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

    2) OR_5, $=NR_5$ o,

    3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y

se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo policíclico divalente, y,

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o

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$NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenileno de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-$\underset{R_{19}}{N}$-R_{18} en donde X_5 es un sol

enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policíclico en donde X_6 se

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selecciona de un solo enlace o alquileno inferior, estos grupos se sustituyen optativamente con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o $X_5-N(R_{19})-R_{18}$ en donde X_5 es un solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;
- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

con la condición de que,

- cuando R_1 es fenilo, lleva por lo menos un sustituyente que no es H,
- cuando X_2 es un solo enlace y tanto R_1 como R'_3 son fenilo, cada uno de R_1 y R'_3 llevan por lo menos un sustituyente que no es H,
- cuando X_2 es un solo enlace y R'_3 es fenilo, R'_3 no se sustituye con un éster o un ácido carboxílico en la posición orto,
- el átomo de R_3 que está unido al grupo tiadiazol es un átomo

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de carbono,

excluyendo los siguientes compuestos,

1-Fenil-1-[4-fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-metanona,

1-[4-Fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-1-tiofen-2-il-metanona,

1-Fenil-1-(4-fenil-5-*p*-tolilimino-4,5-dihidro-[1,3,4]tiadiazol-2-il)-metanona,

Ciclohexil-[3-(2,4,6-tricloro-fenil)-5-(2,3,3-trimetil-ciclopent-1-enilmetil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

2-(3,5-Difenil-3*H*-[1,3,4]tiadiazol-2-ilidenamino)-1,4-difenil-but-2-en-1,4-diona,

Dimetil éster del ácido 2-[3-Fenil-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico,

Dimetil éster del ácido 2-[5-(1-Fenil-metanoil)-3-*p*-tolil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico, y,

Dimetil éster del ácido 2-[3-(4-Cloro-fenil)-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico.

2. Un compuesto de acuerdo con la reivindicación 1, en donde R_1, R_2, R_3 e Y son lo definido en la reivindicación 1 con la condición de que, cuando R_2 es fenilo, no sustituido o sustituido con 1 a 3 cloro o con un metilo, entonces R_3 no representa C(=O)-fenilo, C(=O)-tienilo, fenilo o CH_2-(2,3,3-trimetil-ciclopent-1-enilo).

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3. Un compuesto de la fórmula (I) definido en la reivindicación 1 o 2, en donde porque R_1 es:

alquilo de C_4-C_6,

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace, un heterociclo divalente o un alquileno inferior, y
- R_4 se selecciona de:

1) H, =O, halógeno, CN, haloalquilo inferior, preferentemente CF_3, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=S)NR_9R_{10}$,

en donde R_5 se selecciona de hidrógeno o alquilo inferior, optativamente sustituido con OH, y R_6, R_9 y R_{10} son

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idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior.

4. Un compuesto definido en cualquiera de las reivindicaciones 1 a 3, en donde R_2 es alquilo inferior.

5. Un compuesto definido en cualquiera de las reivindicaciones 1 a 4, en donde R_3 es X_2-R'_3 en donde

- X_2 es solo enlace, alquileno de C_1-C_4, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, y
- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policiclico,

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o alquileno inferior, y
- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5,

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OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

6. Un compuesto definido en cualquiera de las reivindicaciones 1 a 5, en donde R_1 es:

cicloalquilo, preferentemente ciclohexano,

cicloalquenilo,

arilo, preferentemente fenilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferente, en donde:

- X_1 es solo enlace o un heterociclo divalente y,
- R_4 se selecciona de:

1) H, halógeno, CF_3, =O,

2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$.

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en donde R_5 y R_6 son idénticos o diferentes y se seleccionan de hidrógeno o metilo.

7. Un compuesto definido en cualquiera de las reivindicaciones 1 a 6, en donde R_2 es CH_3.

8. Un compuesto definido en cualquiera de las reivindicaciones 1 a 7, en donde R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6, y
- R'_3 es:

cicloalquilo,

arilo, preferentemente fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o $-CH_2-$, y
- R_{17} es:

1) H, CN, CF_3, halógeno, NO_2,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$,

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SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=N-CN)NR_9R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

9. Un compuesto de acuerdo con las reivindicaciones 3, 4, y 5.

10. Un compuesto de acuerdo con las reivindicaciones 6, 7 y 8.

11. Un compuesto definido en la reivindicación 1, en donde R_1 es:

ciclohexano,

fenilo

o un grupo bicíclico;

cada uno optativamente susituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es solo enlace o un heterociclo divalente, y
- R_4 se selecciona de:

1) H, halógeno, CF_3,

2) COOH, OH,

3) $C(=O)NR_7R_8$ en donde R_7 y R_8 son iguales o diferentes y se seleccionan de H o alquilo inferior,

R_2 es CH_3, y

R_3 es X_2-R'_3 en donde

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- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6 y

- R'_3 es:

fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace, y

- R_{17} es:

1) CN, OH, CF_3, =O, alcoxi de C_1-C_6, halógeno,

2) $COOR_5$, SO_2R_5,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 o R_6,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

12. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es S.

13. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es O.

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14. Un compuesto seleccionado del grupo formado por:

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido (1R*, 2R*)-2-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fenil-etanol,

2-{2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-etanol,

{1-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclopentil}-metanol,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2,5,6-trifluoro-benzoico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-propil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclobutil-amina,

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3-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-azepan-2-ona,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclopentil-amina,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-cicloheptil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-3-metil-butan-1-ol,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-metil-propan-1-ol,

terc-Butil-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-isopropil-amina,

Ácido 4-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(1-etil-propil)-amina,

4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,2-diamina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-fluoro-fenil)-amina,

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N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,4-diamina,

(1R*, 2S*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-trifluorometil-fenil)-amina,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

(1-Aza-biciclo[2.2.2]oct-3-il)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

(R)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-fluoro-fenil)-amina,

(3-Cloro-fenil)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ácido {3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-acético,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzamida,

Biciclo[2.2.1]hept-2-il-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

(1R*, 2R*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

5-(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-2-metoxi-fenol,

Ácido 3-(5-ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-4-hidroxi-benzoico,

(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-(3-metanosulfonil-fenil)-amina,

(1R*,2R*)-2-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ciclohexil-[5-(2,4-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(2-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[3-metil-5-(4-trifluorometil-fenil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-piridin-4-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[5-(3-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

Ciclohexil-[5-(3-metoxi-4-nitro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2,4-Dicloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Ciclohexil-(3-metil-5-tiofen-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[5-(3,5-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-[5-(2-etil-5-metil-2H-pirazol-3-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Cloro-2,6-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-(5-isoxazol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[3-metil-5-(5-piridin-2-il-tiofen-2-il)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

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5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-6-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

2-Cloro-5-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dietilamino-etil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-propil)-N-etil-bencenosulfonamida,

Metil éster del ácido [5-(4-Cloro-fenil)-2-ciclohexilimino-[1,3,4]tiadiazol-3-il]-acético,

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Metil éster del ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-hidroxi-etil)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2-diol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,6-dimetoxi-fenol,

6-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-piridin-2-ol,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2,3-triol,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinolin-8-ol,

Ciclohexil-(3-metil-5-pirazin-2-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

5-[(E)-2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-vinil]-2-metoxi-fenol,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol,

Ciclohexil-(3-metil-5-quinolin-8-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

4-(5-Ciclohexilimino-4-methyl-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

[5-(5-Cloro-1H-indol-2-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina; compuesto con ácido trifluoro-metanesulfónico,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

Ciclohexil-[5-(3,4-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Bromo-4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

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Ciclohexil-[5-(4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-fenil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-hidroxi-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Sal de clorhidrato de 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-*N*-(2H-tetrazol-5-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

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Ciclohexil-{5-[4-(1-etil-1H-tetrazol-5-il)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isobutil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-N-metil-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-1-(3-hidroximetil-piperidin-1-il)-metanona,

terc-Butil éster del ácido 2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido 2-({1-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-metanoil}-amino)-3-(4-hidroxi-fenil)-propiónico, compuesto con ácido 2,2,2-trifluoro-acético,

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terc-Butil éster del ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido (S)-2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-piridin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-[4-(4-fluoro-fenil)-piperazin-1-il]-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-pirimidin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-metil-piperazin-1-il)-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(1-etil-pirrolidin-2-ilmetil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-Bencil-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

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N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-1)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

[5-(4-((N-ciano-N'-etilmorfolin)-carboximidamido)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

Ciclohexil-(3-metil-5-piridin-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

(5-Benzo[1,3]dioxol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-ciclohexil-amina,

Ciclohexil-[3-metil-5-(3,4,5-trimetoxi-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

Ácido 5-[5-(4-Ciano-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(cis-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[4-Metil-5-(trans-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

(1R*, 3R*))-3-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ácido 4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

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4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-morfolin-4-il-etil)-benzamida,

Ácido 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

N-terc-Butil-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(1,1-dimetil-3-oxo-butil)-4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(2-Ciano-1,2,2-trimetil-etil)-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Metil éster del ácido 1-{4-[5-((1R*,3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoilamino}-ciclopropanocarboxílico,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-benzamida,

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4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Ácido 5-[5-(4-Carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[4-Metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3,3-Difluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Fluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

(1R*,3R*)-3-{3-Metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-ilidenamino}-ciclohexanol,

Ácido 3-[5-(4-cloro-fenyl)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

Ácido 3-[5-(4-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 2-fluoro-5-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-piperidin-1-il amina,

[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(tetrahidro-piran-4-il)-amina,

Ácido 3-[5-(4-acetilamino-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

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N-{4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{5-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-piridin-2-il}-acetamida,

3-[5-(4-Cloro-fenil)-3-metil-3H/-[1,3,4]tiadiazol-2-ilidenamino]-benzonitrilo,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-N-hidroxi-benzamidina,

3-{3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-metil-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzonitrilo,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzamida,

[5-(4-Bromo-3-metoxi-fenil)-3-metil-2,3-dihidro-[1,3,4]tiadiazol-2-il]-ciclohexil-amina,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-hidroxi-benzamida,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-nitro-benzoico,

Metil éster del ácido 2-amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Metil éster del ácido 2-acetilamino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-1H-quinazolin-2,4-diona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

Metil éster del ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

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Ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[3-metil-5-piridin-2-il-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-Cloro-3-sulfamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-{3-metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-iliden}-amina,

Ciclohexil-[3-metil-5-(4-nitro-fenil)-3H-[1,3,4] tiadiazol-2-iliden]-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenilamina,

[5-(4-(N-ciano-N'-(2-dimetilaminoetil)-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida,

[5-(4-(bis-etilsulfonilamino)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(1-(2-dimetilaminoetil)amino-2-nitro-vinilamino)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

(E)-N^1-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-2-nitro-eten-1,1-diamina,

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[5-(*N*-ciano-*N'*-metil-4-carboximidamido-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(N-ciano-N'-amino-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-amida del ácido etanosulfónico,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-fenil]-urea,

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Metil éster del ácido 2-cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Metil éster del ácido 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzoico y

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzamida

15. Un compuesto de acuerdo con la reivindicación 14, seleccionado del grupo formado por:

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5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

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2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

terc-butil éster del ácido 2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

metil éster del ácido 2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

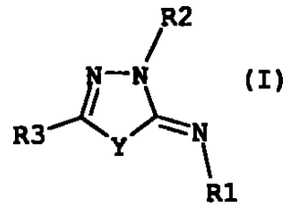
7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida, y

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea.

16. Una composición farmacéutica que comprende un compuesto de la fórmula (I)

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(I)

en donde:

- Y es O o S;

- R_1 es:

alquilo de C_1-C_{10},

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

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3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,.

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es X_2-R'_3 en donde:

- X_2 es un solo enlace o,

un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-

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C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo heterocíclico divalente, y

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, bioisóstero de ácido carboxílico, cicloalquilo,

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2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

en donde,

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenilo de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-$N(R_{18})(R_{19})$

en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

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- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policiclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos optativamente se sustituyen con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o $X_5-N(R_{19})-R_{18}$ en donde X_5 es un solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

junto con un portador farmacéuticamente aceptable,

con la condición de que el compuesto de la fórmula (I) no sea etil éster del ácido 4-[2-Formilimino-5-(4-metoxi-fenil)-[1,3,4] tiadiazol-3-il]-butírico, o

etil éster del ácido 4-[5-(4-cloro-fenil)-2-formilimino-[1,3,4]tiadiazol-3-il]-butírico.

17. Una composición farmacéutica de acuerdo con la reivindicación 16, que comprende un compuesto de la fórmula (I), en donde R_1, R_2, R_3 e Y son lo definico en la

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reivindicación 18, con la condición de que cuando R_1 es C(=O)-H, R_2 no represente $(CH_2)_3$-C(=O)OCH_2CH_3.

18. Una composición farmacéutica que comprende un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, junto con un portador farmacéuticamente aceptable.

19. Una composición farmacéutica de acuerdo con la reivindicación 16, 17 o 18, para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante.

20. Un método para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante, que comprende administrar a un mamífero, particularmente a un humano, que lo necesita, una cantidad eficaz de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15.

21. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se debe tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades

endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

22. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

24. El uso de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, para la fabricación de un medicamento para el tratamiento de enfermedades para las cuales el tratamiento con un inhibidor de PDE7 es relevante.

24. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

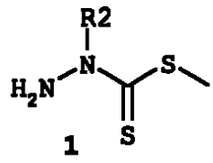
25. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de dolor

visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

26. Un compuesto de la fórmula (I), definido en cualquiera de las reivindicaciones 1 a 15, como medicamento.

27. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

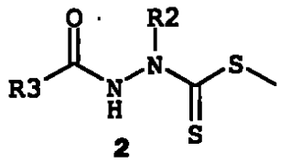
(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reividindicación 1, con disulfuro de carbono y MeX donde X es un grupo saliente para obtener un compuesto de la fórmula 1



1

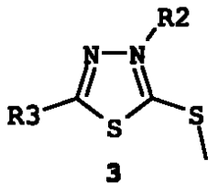
(b) reacción del S-metilditiocarbazato 1 con un cloruro de acilo R_3COCl en donde R_3 es lo definido en la reivindicación 1 para obtener un metilditiocarbazato acilado 2

00927



2

(c) ciclación del metilditiocarbazato acilado 2 en un 1,3,4-tiadiazol 3



3

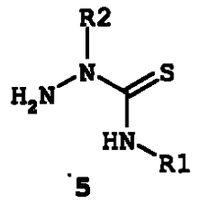
(d) reacción del 1,3,4-tiadiazol 3 con una amina R_1NH_2 en donde R_1 es lo definido en reivindicación 1, para obtener el compuesto de la fórmula (I) en donde Y es S,

(e) aislación del compuesto de la fórmula (I).

28. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

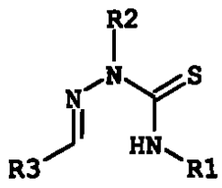
(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$ en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5

00923 408



5

(b) reacción de la tiosemicarbazida 5 con un aldehído R_3CHO en donde R_3 es lo definido en la reivindicación 1, para obtener la tiosemicarbazona 6



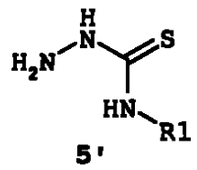
(c) ciclación de la tiosemicarbazona 6 en el compuesto de la fórmula (I) en donde Y es S,

(d) aislación del compuesto de la fórmula (I).

29. El proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

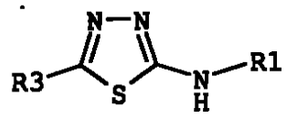
(a) reacción de un ácido carboxílico R_3COOH en donde R_3 es lo definido en reivindicación 1, con la siguiente tiosemicarbazida 5'

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5'

para obtener el 1,3,4-tiadiazol 7



7

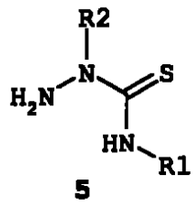
(b) reacción del 1,3,4-tiadiazol 7 con R_2X, en donde R_2 es lo definido en la reivindicación 1 y X es un grupo saliente para obtener el compuesto de la fórmula (I) en donde Y es S

(c) aislación del compuesto de la fórmula (I).

30. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 14, que comprende los siguientes pasos:

(a) reacción de un ácido carboxílico R_3COOH, en donde R_3 es lo definido en la reivindicación 1, con la siguiente tiosemicarbazida 5

0093? 910



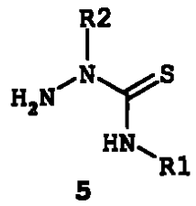
5

para obtener el compuesto final de la fórmula I en donde Y es S,

(b) aislación del compuesto de la fórmula (I).

31. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 11 o 13, en donde Y es S, que comprende los siguientes pasos:

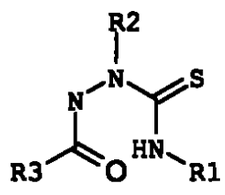
(a) reacción de una hidrazina sustituida R_2NHNH_2, en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$, en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5,



5

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(b) reacción de la tiosemicarbazida 5 con R_3-C(=O)Cl, en donde R_3 es lo definido en la reivindicación 1, para formar la tiosemicarbazida 8 deseada



8

(c) ciclación de la tiosemicarbazida 8 en el compuesto final de la fórmula I en donde Y es O,

(d) aislación del compuesto de la fórmula (I).

912 536

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INFORME DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No PCT/EP 01/11330.

A. CLASIFICACION DEL OBJETO:

IPC 7

C07D285/135 C07D271/113 C07D417/04 C07D417/10 C07D417/12 C07D417/14 C07D453/02 A61K31/433 A61K31/55 A61K31/439 A61K31/4245 A61K31/4439 A61K31/4709 A61K31/497 A61P29/00

De acuerdo con la Clasificación Internacional de Patentes (IPC) o IPC y clasificación nacional.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por símbolos de clasificación)

I.P.C 7 C07D A61K A61P

Otros documentos buscados que no sea la documentación mínima al punto que dichos documentos se incluyen en los campos buscados: [Aparece un espacio en blanco]

Base de datos electrónica consultada durante la búsqueda internacional(nombre de la base de datos y, donde sea práctico, términos de búsqueda utilizados):

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS

5

C. DOCUMENTOS CONSIDERADOS RELEVANTES

CATEGORIA*	Citación del documento, con indicación, cuando fuera adecuado, de los pasajes relevantes	Relevante a la reivindicación No.
X	CHEMICAL ABSTRACTS, vol. 120, no. 25, 20 de junio de 1994 (1994-06-20), Columbus, Ohio, US; Resumen no. 323458w, EL-FEKY S A ET AL: "Synthesis and biological activity of novel quinazolinones derived from 2-hydrazino-3-phenyl-4(3H)-quinazolinones" página 907; XP002162034, resumen -& DATABASE CPLUS 'Online! Chemical Abstracts Services; No. De ingreso a la base de datos 1994:323458 XP002162039 * RN 155389-95-0 y 155389-96-1 * & ZHONGHUA YAOXUE ZAZHI, vol. 45, no. 4, 1993, páginas	16-19

	303-308, --- -/--	

[x] En la continuación del casillero C se enumeran otros documentos.

[x] En el anexo se enumeran los miembros de la familia de patentes.

* Categorías especiales de los documentos citados:

"A" documento que define el estado general de la materia que no se considera de especial relevancia.

"E" documento anterior pero publicado en la fecha de presentación internacional o después de la misma.

"L" documento que puede provocar dudas con respecto a la(s) reivindicación de prioridad o que se cita para establecer la fecha de publicación de otra citación o por otra razón especial (según se especifique)

"O" documento que se refiere a una divulgación oral, uso, exhibición u otro medio.

"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.

"T" documento tardío publicado después de la fecha de presentación internacional o de la fecha de prioridad y sin conflictos con la solicitud pero citado para comprender el principio o teoría sustentada por la invención.

"X" documento de particular relevancia; la invención reivindicada no puede considerarse novedosa, o que posee mérito inventivo, cuando se considera el documento por sí solo.

"Y" documento de particular relevancia; la invención reivindicada no puede considerarse que posee mérito inventivo cuando el documento se combina con otro u otros de dichos documentos, tal combinación resulta obvia para los expertos en el arte.

"&" documento miembro de la misma familia de patentes.

Fecha de finalización efectiva de la búsqueda internacional:

10 de diciembre de 2001

Fecha de envío del informe de búsqueda internacional:

21/12/2001

Nombre y dirección postal de la ISA

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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl

Fax: (+31-70) 340-3016

Funcionario autorizado: Allard, M

INFORME DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No PCT/EP 01/11330.

A. CLASIFICACION DEL OBJETO:

IPC 7 A61P37/00

De acuerdo con la Clasificación Internacional de Patentes(IPC) o IPC y clasificación nacional.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por símbolos de clasificación)

[en blanco]

Otros documentos buscados que no sea la documentación mínima al punto que dichos documentos se incluyen en los campos buscados:[en blanco]

Base de datos electrónica consultada durante la búsqueda internacional(nombre de la base de datos y, donde sea práctico, términos de búsqueda utilizados):

C. DOCUMENTOS CONSIDERADOS RELEVANTES

[redacted]

CATEGORIA*	Citación del documento, con indicación, cuando fuera adecuado, de los pasajes relevantes	Relevante a la reivindicación No.
X	DD 251 979 A (PÄDAGOGISCHE HOCHSCHULE "DR. THEODOR NEUBAUER" ERFURT/MÜHLHAUSEN) 2 de diciembre de 1987 (1987-12-02) todo el documento ---	1-11,13,31
X	HUISGEN R ET AL: "1.3-Dipolare Cycloadditionen. VI. Anlagerung de Nitrilimine an azomethine und Isocyanate" CHEMISCHE BERICHTE, Vol. 97, no. 4, 3 de abril de 1964 (1964-04-03), páginas 1085-1095, XP002185163 el documento completo, en particular la página 1087, compuesto XXVI --- -/--	1-11, 13, 31

[x] En la continuación del casillero C se enumeran otros documentos.

[x] En el anexo se enumeran los miembros de la familia de patentes.

* Categorías especiales de los documentos citados:

"A" documento que define el estado general de la materia que no se considera de especial relevancia.

"E" documento anterior pero publicado en la fecha de presentación internacional o después de la misma.

"L" documento que puede provocar dudas con respecto a la(s) reivindicación de prioridad o que se cita para establecer la fecha de publicación de otra citación o por otra razón especial (según se especifique)

"O" documento que se refiere a una divulgación oral, uso, exhibición u otro medio.

"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.

"T" documento tardío publicado después de la fecha de presentación internacional o de la fecha de prioridad y sin conflictos con la solicitud pero citado para comprender el principio o teoría sustentada por la invención.

"X" documento de particular relevancia; la invención reivindicada no puede considerarse novedosa, o que posee mérito inventivo, cuando se considera el documento por sí solo.

"Y" documento de particular relevancia; la invención reivindicada no puede considerarse que posee mérito inventivo cuando el documento se combina con otro u otros de dichos documentos, tal combinación resulta obvia para los expertos en el arte.

"&" documento miembro de la misma familia de patentes.

Fecha de finalización efectiva de la búsqueda internacional: 10 de diciembre de 2001

923 SYS
00948

Fecha de envío del informe de búsqueda internacional:

[en blanco]

Nombre y dirección postal de la ISA

Oficina de Patentes Europea, P.B. 5818 Patentlaan 2

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Fax: (+31-70) 340-3016

Funcionario autorizado: Allard, M

924 548

00944

Formulario PCT/ ISA/210 (segunda página) (julio de 1992)

INFORME DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No PCT/EP 01/11330.

C. (continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

CATEGORIA*	Citación del documento, con indicación, cuando fuera adecuado, de los pasajes relevantes	Relevante a la reivindicación No.
X	L'ABBÉ G ET AL: "Synthesis and decomposition of functionalized diaziridinimines" JOURNAL O FORGANIC CHEMISTRY, vol. 46, no. 22, 23 de octubre de 1981 (1981-10-23) páginas 4478-4481, XP002185164 el documento completo, en particular la página 4479, compuesto 15b	1-11,13,31

X	CHEMICAL ABSTRACTS, vol. 73, no. 11, 14 de septiembre de 1970 (1970-09-14) Columbus, Ohio, US; Resumen no. 56035q, GEHLEN H ET AL: "2-Amino-1,3,4-oxadiazoles.	1-11, 13, 31

926 580

0024

XXXV.

Síntesis and reaction of

1,3,4-oxadiazolo´3,2-

a!pyrimidinones"

Página 322;

XP002185165

Resumen

& ARCH PHARM (WEINHEIM)

vol. 303, no. 6, 1970,

páginas 501-510

X	AWASTHI A K AND AL: "A new route to 2,3,5-trisubstituted 2,3-dihidro-1,3,4-oxadiazoles via stabilized sulfuranes" SYNTESIS, No. 7, julio de 1984 (1984-07), páginas 590-591 XP002185166 el documento completo	1-11, 13, 31
A	WO 99 42089 A (ROCHE DIAGNOSTICS GMBH) 26 de agosto de 1999 (1999-08-26) el documento completo ---	1,20-25
A	DE 37 17 232 A (VEB DEUTSCHES HYDRIERWERK RODLEBEN) 8 de diciembre de 1988 (1988-12-08) el documento completo ---	1, 20-25

INFORME DE BÚSQUEDA INTERNACIONAL

Información sobre los miembros de la familia de patentes

Solicitud internacional No. PCT/EP01/11330

Documento de patente citado en el informe de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
DD 251979 A	02-12-1987	DD 251979 A1	02-12-1987
WO 9942089 A	26-08-1999	AU 2926099 A	06-09-1999
		WO 9942089 A2	26-08-1999
		EP 1054669 A2	29-11-2000
DE 3717232 A	08-12-1988	DD 247003 A1	24-06-1987
		DE 3717232 A1	08-12-1988
		JP 1031788 A	02-02-1989

Formulario PCT/ISA/210 (anexo de familia de patentes) (julio de 1992)

Legal Division, Patents Dept.
Pfizer
3-9, rue de la Loge – BP 100
F-94265 Fresnes Cedex
Tél. : 01 40 96 32 31 ou 01 40 96 76 97
Fax : 01 40 96 76 90

4/60 SEP 930

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P.B. 5818
PATENTLAAN2
NL-2280 HV RIJSWIJK (ZH)
THE NETHERLANDS

October 25th, 2002

Fax: +31 70 340 3016
& mail confirmation

Our ref.: 018155 (A-305)
DH/MB

Re: International application No. PCT/EP01/11330
Applicant : Warner-Lambert Company

Dear M. Allard,

Please find enclosed two sets of amended claims, one of which comprising underlined amendments. The amendments are detailed below.

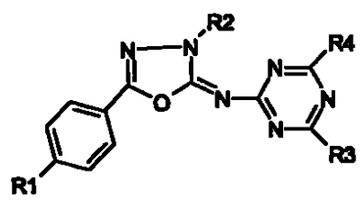
The examiner has considered that claims 1-11, 13 and 31 lack novelty in view of D1, D2 (in particular page 1087 compound XXVI), D3 (in particular page 4479, compound 15b), D4 and D5.

Please note that:
- D1 is not relevant to claims 6, 10 and 11 as R1 cannot represent an heterocycle in said claims,
- D2 is not relevant to claims 4, 7, 9, 10 and 11 as R2 cannot represent a phenyl group in said claims,
- D3 is not relevant to claims 6, 10 and 11 as R1 cannot represent a tert-butyl group in said claims,
- D3 is not relevant to claims 7 as R2 cannot represent a tert-butyl group in said claim,
- D4 is not relevant to claim 3, 6, 9, 10 and 11 as R1 cannot represent an alkenyl group in said claims,
- D5 is not relevant to claims 4, 7, 9, 10 and 11 as R2 cannot represent a phenyl in said claims,
- D5 is not relevant to claims 5 and 8 as R3 cannot represent a group C(=O)-phenyl in said claims.

Please find below our comments relative to D1 to D5:

D1: DD251979 (1987)

D1 discloses compounds of formula



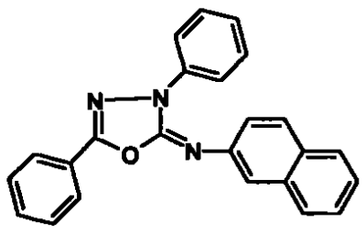
wherein R1 and R2 are selected from alkyl or aryl and R3 and R4 are selected from alkoxy, aryloxy, alkylthio, arylthio, alkylamino, arylamino, dialkylamino, diarylamino, alkylarylamino, optionally substituted hydrazine or OH, Cl.

In order to overcome the examiner's objection, the following disclaimer has been added in claim 1:

"When R3 represents a substituted phenyl and Y is O, then R1 is other than substituted 1,3,5-triazine"

D2: Huisgeb R et al, 1964, chemische berite:

D2 discloses the following compound

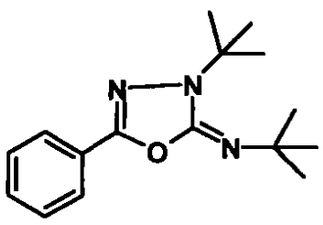


XXVI

A proviso has been added in claim 1 to disclaim compound XXVI.

D3: L'abbé G et al Journ of org chem.. 1981

D3 discloses:

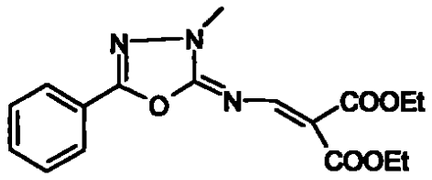


compound 15b

A proviso has been added in claim 1 to disclaim this compound.

D4: CA vol 73 no 11 (1970)

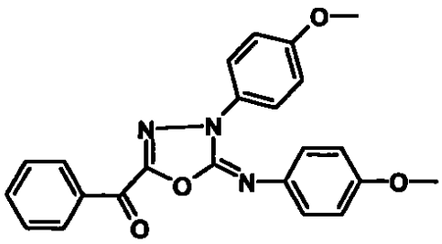
D4 discloses compound IX:



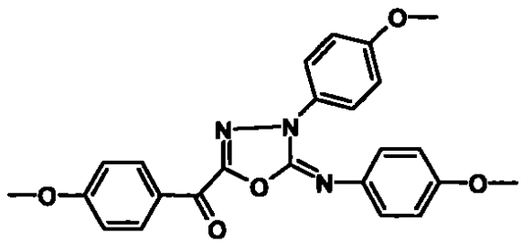
A proviso has been added in claim 1 to disclaim this compound.

D5: Awasthi (1984)

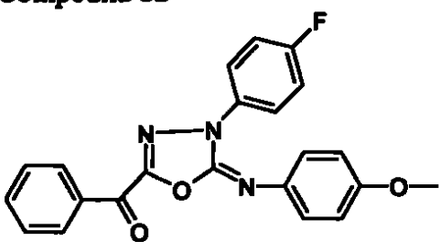
D5 disclosed 3 oxadiazoles:



Compound 8a



Compound 8b



Compound 8c

A proviso has been added in claim 1 to disclaim these compounds.

The above amendments should overcome all the objections raised by the examiner. If the examiner has further objections, we would like to receive a detailed "written opinion".

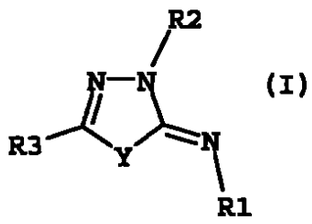
Sincerely yours,

Denise Hirsch
European Patent Attorney

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CLAIMS

1. A compound having the following formula (I),



in which

- Y is O or S;
- R1 is:
  - C_4-C_{10} alkyl,
  - C_2-C_{10} alkenyl,
  - C_2-C_{10} alkynyl,
  - cycloalkyl,
  - cycloalkenyl,
  - heterocycle,
  - aryl,
  - or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are

selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_4-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
2) $COOR_5$, OR_5, SO_2R_5,
3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
    2) OR_5, $=NR_5$ or,
    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=N\text{-}SO_2NH_2)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$
  4) heterocycle optionally substituted with one or several groups R_5;

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl

optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;

- X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;

- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

with the proviso that,

- when R1 is phenyl, it bears at least one substituent other than H,

- when X_2 is a single bond and both R1 and R'_3 are phenyl, each of R1 and R'_3 bear at least one substituent other than H,

- when X_2 is a single bond and R'_3 is phenyl, R'_3 is not substituted by an ester or a carboxylic acid in the ortho position,

- When R3 represents a substituted phenyl and Y is O, then R1 is other than a substituted 1,3,5-triazine,

- the atom of R3 which is linked to the thiadiazole group is a carbon atom,

with the exclusion of the following compounds,

(3,5-diphenyl-3H-[1,3,4]oxadiazol-2-ylidene)-naphthalen-2-yl-

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amine,
tert-butyl-(3-tert-butyl-5-phenyl-3*H*-[1,3,4]oxadiazol-2-ylidene)-amine,
2-[(3-methyl-5-phenyl-3H-[1,3,4]oxadiazol-2-ylideneamino)-methylene]-malonic acid diethyl ester,
[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]phenyl-methanone,
(4-methoxy-phenyl)-[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-methanone,
[4-(4-fluoro-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl-methanone,
1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-methanone,
1-[4-Phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,
1-Phenyl-1-(4-phenyl-5-*p*-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,
Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethyl-cyclopent-1-enylmethyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
2-(3,5-Diphenyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,
2-[3-Phenyl-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,
2-[5-(1-Phenyl-methanoyl)-3-*p*-tolyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,
2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

2. A compound according to claim 1 in which R1, R2, R3 and Y are as defined in claim 1 with the proviso that, when R2 is a phenyl, unsubstituted or substituted whith 1 to 3 chorine or with a methyl, then R3 does not represent C(=O)-phenyl, C(=O)-thienyl, phenyl or CH_2-(2,3,3-trimethyl-cyclopent-1-enyl).

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3. A compound of formula (I) as defined in claim 2, in which R1 is:

C_4-C_6 alkyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:
  1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$,
  wherein R_5 is selected from hydrogen or lower alkyl, optionally substituted with OH, and R_6, R_9 and R_{10} are identical or different and are selected from hydrogen or lower alkyl.

4. A compound as defined in any one of claims 1 to 3 in which R2 is lower alkyl.

5. A compound as defined in any one of claims 1 to 4 in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, and,
- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

6. A compound as defined in any one of claims 1 to 5, in which R1 is:
cycloalkyl, preferably cyclohexane,
cycloalkenyl,
aryl, preferably phenyl,
or a bicyclic group;
each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$.
  wherein R_5 and R_6 are identical or different and are selected from hydrogen or methyl.

7. A compound as defined in any one of claims 1 to 6, in which R2 is CH_3.

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8. A compound as defined in any one of claims 1 to 7 in which R3 is X_2-R'$_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl,
heterocycle,
or a polycyclic group;
each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or -CH_2-, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N\text{-}CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

9. A compound according to claims 3, 4 and 5.

10. A compound according to claims 6, 7 and 8.

11. A compound as defined in claim 1 in which R1 is:

cyclohexane,
phenyl
or a bicyclic group;
each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3,

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2) COOH, OH,

3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same or different and are selected from H or lower alkyl,

R2 is CH_3, and,

R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond, and,
- R_{17} is:

1) CN, OH, CF_3, =O, C_1-C_6 alkoxy, halogen,

2) $COOR_5$, SO_2R_5,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 or R_6,

4) heterocycle optionally substituted with one or several groups R_5.

12. A compound as defined in any one of claims 1 to 11 in which Y is S.

13. A compound as defined in any one of claims 1 to 11 in which Y is O.

14. A compound selected from the group consisting of:
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol,

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2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol,
{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-propyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol,
tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-isopropyl-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine,

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine,
(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine,
3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine,
(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide,
Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol,
3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid,

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(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine,
(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[5-(3-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

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5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol,
compound with trifluoro-methanesulfonic acid
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,

2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide,
[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol,
6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol,
Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol,
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-*N*-(2H-tetrazol-5-yl)-benzamide hydrochloride salt,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
2-({1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-methanoyl}-amino)-3-(4-hydroxy-phenyl)-propionic acid, compound with 2,2,2-trifluoro-acetic acid,

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(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,
N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,

[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,

Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,

(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine,

Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

5-[5-(4-Cyano-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,

4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester,
4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
(1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,

3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,

[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine,

[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine,

3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,

N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide,

3-[5-(4-Chloro-phenyl)-3-methyl-3H/-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile,

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine,

3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-methyl-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide,

[5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine,
[5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide,
[5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
(E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine,
[5-(*N*-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-urea,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester, and,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide.

15. A compound according to claim 14, selected from the group consisting of:

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-

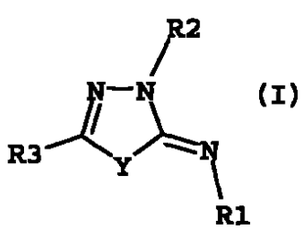
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[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-
yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-
benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-
benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-
benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-
phenyl)-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-
phenyl)-propionic acid; compound with 2,2,2-trifluoro-
acetic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-
benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-
propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,

N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide, and,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea.

16. Pharmaceutical composition comprising a compound of formula (I),



wherein:

- Y is O or S;
- R1 is:

C_1-C_{10} alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a polycyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:

a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or a divalent heterocycle, and,

- R_4 is:

1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:

lower alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,

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aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'$_3$ wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
    2) OR_5, $=NR_5$ or,
    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:
    cycloalkyl,
    cycloalkenyl,
    aryl,
    heterocycle,
    or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene, a divalent heterocycle or a divalent polycyclic group, and,

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- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5;

wherein,

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-$N(R_{19})$-R_{18} in which X_5 is a single bond or lower alkyl and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;
  - X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or

several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;
- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier, with the proviso that the compound of formula (I) is not 4-[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-butyric acid ethyl ester, or, 4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-butyric acid ethyl ester.

17. A pharmaceutical composition according to claim 16, comprising a compound of formula (I), in which R1, R2, R3 and Y are as defined in claim 18, with the proviso that when R1 is C(=O)-H, then R2 does not represent $(CH2)_3$-C(=O)OCH_2CH_3.

18. Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 15, together with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to claim 16, 17 or 18, for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant.

20. Method for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant, comprising administering to a mammal, particularly a human, in need thereof, an effective amount of compound of formula (I) according any of claims 1 to 15.

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21. Method according to claim 20, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

22. Method according to claim 20, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

23. Use of a compound of formula (I) according to any one of claims 1 to 15, for the manufacture of a medicament for the treatment of diseases for which treatment by a PDE7 inhibitor is relevant.

24. Use according to claim 23, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

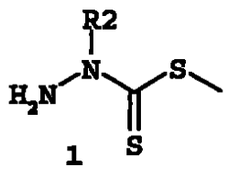
25. Use according to claim 23, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

26. A compound of formula (I) as defined in any one of claims 1 to 15, as a medicament.

27. A process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15 in which Y is S, comprising the following steps:

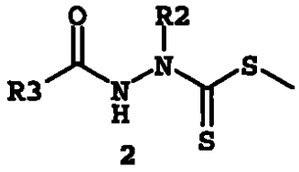
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(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with carbon disulphide and MeX where X is a leaving group to obtain a compound of formula 1



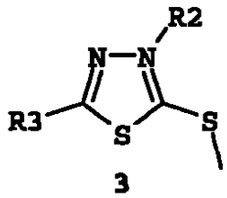
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(b) reaction of the S-methyldithiocarbazate 1 with an acyl chloride R3COCl in which R3 is as defined in claim 1 to to obtain an acylated methyldithiocarbazate 2



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(c) cyclization of the acylated methyldithiocarbazate 2 into a 1,3,4-thiadiazole 3



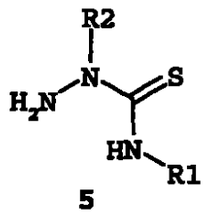
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(d) reaction of the 1,3,4-thiadiazole 3 with an amine $R1NH_2$ in which R1 is as defined in claim 1, to obtain the compound of formula (I) in which Y is S,

(e) isolating the compound of formula (I).

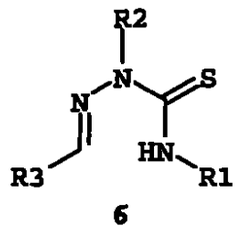
28. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1 in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5



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(b) reaction of the thiosemicarbazide 5 with an aldehyde R3CHO in which R3 is as defined in claim 1, to obtain the thiosemicarbazone 6



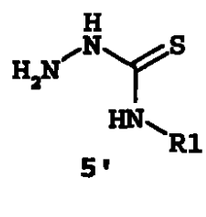
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(c) cyclization of the thiosemicarbazone 6 into the compound of formula (I) in which Y is S,

(d) isolating the compound of formula (I).

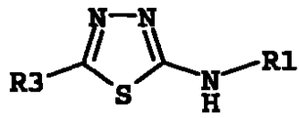
29. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH in which R3 is as defined in claim 1, with the following thiosemicarbazide 5'



5'

to obtain the 1,3,4-thiadiazole 7



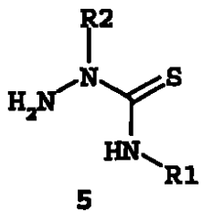
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(b) reaction of the 1,3,4-thiadiazole 7 with R2X, in which R2 is as defined in claim 1 and X is a leaving group to obtain the compound of formula (I) in which Y is S

(c) isolating the compound of formula (I).

30. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH, in which R3 is as defined in claim 1, with the following thiosemicarbazide 5



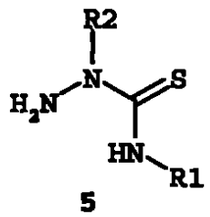
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to obtain the final compound of formula I in which Y is S,

(b) isolating the compound of formula (I).

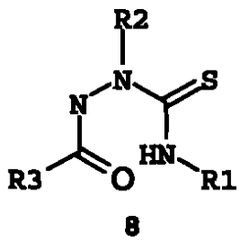
31. Process for the preparation of a 1,3,4-oxadiazole of formula (I) according to any one of claims 1 to 11 or 13, in which Y is O, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$, in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1, in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5,



5

(b) reaction of the thiosemicarbazide 5 with R3-C(=O)Cl, in which R3 is as defined in claim 1, to form the desired thiosemicarbazide 8



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(c) cyclization of the thiosemicarbazide 8 into the final compound of formula I in which Y is O,

(d) isolating the compound of formula (I).

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[en el margen superior izquierdo aparece el logo de Pfizer]

División Legales, Departamento de Patentes

Pfizer

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PAÍSES BAJOS

25 de octubre de 2002

Fax: +31 70 340 3016

& confirmación via e-mail

Nuestra Ref: 018155 (A-305)

DH/MB

Re: Solicitud internacional No. PCT/EP01/11330

Solicitante: Warner-Lambert Company

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Estimado M. Allar,

Sírvase encontrar adjuntos dos pliegos de reivindicaciones enmendadas, uno de ellos con las enmiendas subrayadas. Las enmiendas se detallan a continuación.

El examinador consideró que las reivindicaciones -11, 13 y 31 carecen de novedad en vista de D1, D2 (en particular la página 1087 compuesto XXVI), D3 (en particular la página 4479, compuesto 15b), D4 y D5.

Tenga a bien observar lo siguiente:

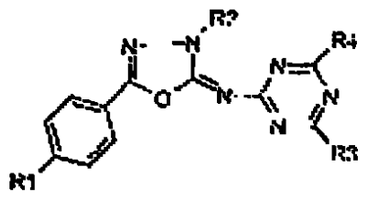
- D1 no es relevante a las reivindicaciones 6, 10 y 11 ya que R1 no puede representar un heterociclo en tales reivindicaciones,
- D2 no es relevante a las reivindicaciones 4, 7, 9, 10 y 11 dado que R2 no puede representar un grupo fenilo en tales reivindicaciones,
- D3 no es relevante a las reivindicaciones 6, 10 y 11 dado que R1 no puede representar un grupo ter-butilo en tales reivindicaciones,
- D3 no es relevante a la reivindicación 7 dado que R2 puede representar un grupo ter-butilo en tal reivindicación,

- D4 no es relevante a las reivindicaciones 3, 6, 9, 10 y 11 dado que R1 no puede representar un grupo alquenilo en tales reivindicaciones,
- D5 no es relevante a las reivindicaciones 4, 7, 9, 10 y 11 dado que R2 no puede representar un fenilo en tales reivindicaciones,
- D5 no es relevante a las reivindicaciones 5 y 8 dado que R3 no puede representar un grupo C(=O)-fenilo en tales reivindicaciones.

Sírvase encontrar a continuación nuestros comentarios con relación a D1-D5.

D1: DD251979 (1987)

D1 revela compuestos de fórmula



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[aparece una frase en un tercer idioma]

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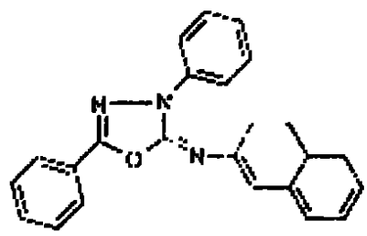
en donde R1 y R2 se seleccionan de alquilo o arilo y R3 y R4 se seleccionan de alcoxi, ariloxi, alquiltio, ariltio, alquilamino, arilamino, dialquilamino, diarilamino, alquilarilamino, opcionalmente hidrazina sustituida o OH, Cl.

Con el fin de superar las objeciones del examinador, se ha incorporado el siguiente descargo en la reivindicación 1:

"cuando R3 representa un fenilo susituido e Y es O, entonces R1 es diferente de 1,3,5-triazina sustituida"

D2: Huisgeb R et al, 1964, chemische berite:

D2 revela el siguiente compuesto



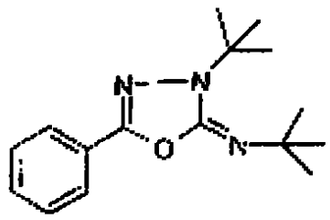
XXVI

9x2

se agregó una condición en la reivindicación 1 para renunciar al compuesto XXVI

D3: L´abbé G et al Journ of org chem. 1981

D3 revela:

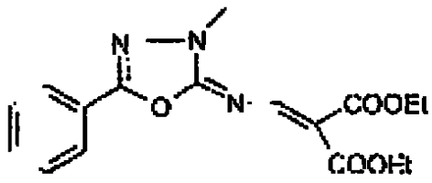


compuesto 15b

se agregó una condición en la reivindicación 1 para renunciar a tal compuesto.

D4: CA vol 73 no 11 (1970)

D4 revela el compuesto IX:

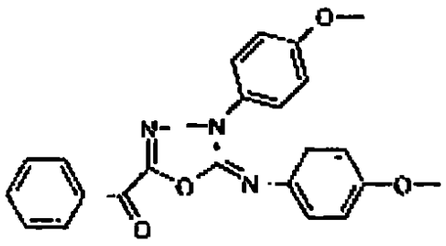


se agregó una condición en la reivindicación 1 para renunciar a tal compuesto.

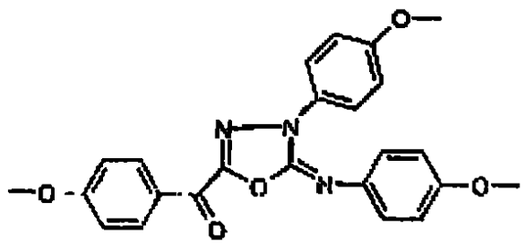
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D5: Awasthi (1984)

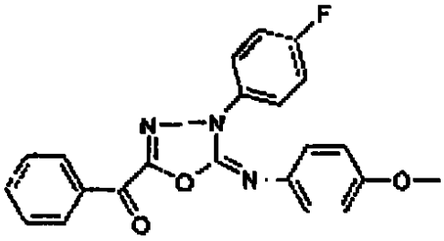
D5 revelaba 3 oxadiazoles:



Compuesto 8a



Compuesto 8b



Compuesto 8c

Se agregó una condición en la reivindicación 1 para renunciar a tales compuestos.

Las enmiendas precedentes deben superar las objeciones del examinador. Si éste llegara a tener otras objeciones, agradeceremos recibir una "opinión escrita" detallada.

Atentamente,

[firma ilegible]

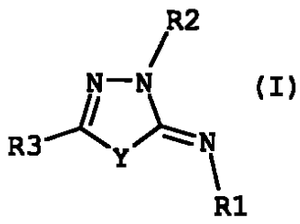
Denise Hirsch

Abogada de patentes europea.

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REIVINDICACIONES

1. Un compuesto que tiene la siguiente fórmula (I),



(I)

en donde

- Y es O o S;

- R_1 es:

  alquilo de C_4-C_{10},

  alquenilo de C_2-C_{10},

  alquinilo de C_2-C_{10},

  cicloalquilo,

  cicloalquenilo,

  heterociclo,

  arilo,

  o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

  un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y,

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_4-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es X_2-R'_3 en donde:
  - X_2 es un solo enlace o,

    un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

    1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

    2) OR_5, $=NR_5$ o,

    3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'3 es:

  cicloalquilo,

  cicloalquenilo,

  arilo,

  heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo policíclico divalente, y,

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

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- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenileno de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-N(R_{18})(R_{19}) en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policíclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos se sustituyen optativamente con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o X_5-N(R_{18})(R_{19}) en donde X_5 es un solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o

diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

con la condición de que,

- cuando R_1 es fenilo, lleva por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y tanto R_1 como R'_3 son fenilo, cada uno de R_1 y R'_3 llevan por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y R'_3 es fenilo, R'_3 no se sustituye con un éster o un ácido carboxílico en la posición orto,

- cuando R_3 representa un fenilo sustituido e Y es o, entonces R_1 es diferente de 1,3,5-triazina sustituida,

- el átomo de R_3 que está unido al grupo tiadiazol es un átomo de carbono,

excluyendo los siguientes compuestos,

(3,5-difenil-3H-[1,3,4]oxadiazol-2-iliden)-naftalen-2-il-amina,

terc-butil-(3-terc-butil-5-fenil-3H-[1,3,4]oxadiazol-2-iliden)-amina,

dietil éster del ácido 2-[(3-metil-5-fenil-3H-[1,3,4]oxadiazol-2-ilidenamino)-metilen]-malónico,

[4-(4-metoxi-fenil)-5-(4-metoxi-fenilamino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]fenil-metanona,

(4-metoxi-fenil)-[4-(4-metoxi-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-metanona,

[4-(4-fluoro-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-fenil-metanona,

1-Fenil-1-[4-fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-metanona,

1-[4-Fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-1-tiofen-2-il-metanona,

1-Fenil-1-(4-fenil-5-*p*-tolilimino-4,5-dihidro-[1,3,4]tiadiazol-2-il)-metanona,

Ciclohexil-[3-(2,4,6-tricloro-fenil)-5-(2,3,3-trimetil-ciclopent-1-enilmetil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

2-(3,5-Difenil-3*H*-[1,3,4]tiadiazol-2-ilidenamino)-1,4-difenil-but-2-en-1,4-diona,

Dimetil éster del ácido 2-[3-Fenil-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico,

Dimetil éster del ácido 2-[5-(1-Fenil-metanoil)-3-*p*-tolil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico, y,

Dimetil éster del ácido 2-[3-(4-Cloro-fenil)-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico.

2. Un compuesto de acuerdo con la reivindicación 1, en donde R_1, R_2, R_3 e Y son lo definido en la reivindicación 1 con la

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condición de que, cuando R_2 es fenilo, no sustituido o sustituido con 1 a 3 cloro o con un metilo, entonces R_3 no representa C(=O)-fenilo, C(=O)-tienilo, fenilo o CH_2-(2,3,3-trimetil-ciclopent-1-enilo).

3. Un compuesto de la fórmula (I) definido en la reivindicación 1 o 2, en donde porque R_1 es:

alquilo de C_4-C_6,

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo biciclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace, un heterociclo divalente o un alquileno inferior, y
- R_4 se selecciona de:

1) H, =O, halógeno, CN, haloalquilo inferior, preferentemente CF_3, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$,

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SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=S)NR_9R_{10}$,

en donde R_5 se selecciona de hidrógeno o alquilo inferior, optativamente sustituido con OH, y R_6, R_9 y R_{10} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior.

4. Un compuesto definido en cualquiera de las reivindicaciones 1 a 3, en donde R_2 es alquilo inferior.

5. Un compuesto definido en cualquiera de las reivindicaciones 1 a 4, en donde R_3 es X_2-R'_3 en donde

- X_2 es solo enlace, alquileno de C_1-C_4, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, y
- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico,

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o alquileno inferior, y
- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno,

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cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

6. Un compuesto definido en cualquiera de las reivindicaciones 1 a 5, en donde R_1 es:

cicloalquilo, preferentemente ciclohexano,

cicloalquenilo,

arilo, preferentemente fenilo,

o un grupo biciclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferente, en donde:

- X_1 es solo enlace o un heterociclo divalente y,
- R_4 se selecciona de:

1) H, halógeno, CF_3, =O,

2) $COOR_5$, OR_5,

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3) $C(=O)NR_5R_6$.

en donde R_5 y R_6 son idénticos o diferentes y se seleccionan de hidrógeno o metilo.

7. Un compuesto definido en cualquiera de las reivindicaciones 1 a 6, en donde R_2 es CH_3.

8. Un compuesto definido en cualquiera de las reivindicaciones 1 a 7, en donde R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6, y
- R'_3 es:

cicloalquilo,

arilo, preferentemente fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o $-CH_2-$, y
- R_{17} es:

1) H, CN, CF_3, halógeno, NO_2,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o

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diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=N-CN)NR_9R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

9. Un compuesto de acuerdo con las reivindicaciones 3, 4, y 5.

10. Un compuesto de acuerdo con las reivindicaciones 6, 7 y 8.

11. Un compuesto definido en la reivindicación 1, en donde R_1 es:

ciclohexano,

fenilo

o un grupo bicíclico;

cada uno optativamente susituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es solo enlace o un heterociclo divalente, y
- R_4 se selecciona de:

1) H, halógeno, CF_3,

2) COOH, OH,

3) $C(=O)NR_7R_8$ en donde R_7 y R_8 son iguales o diferentes y se seleccionan de H o alquilo inferior,

R_2 es CH_3, y

R_3 es X_2-R'_3 en donde

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- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6

y

- R'_3 es:

fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace, y
- R_{17} es:

1) CN, OH, CF_3, =O, alcoxi de C_1-C_6, halógeno,

2) $COOR_5$, SO_2R_5,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 o R_6,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

12. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es S.

13. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es O.

14. Un compuesto seleccionado del grupo formado por:

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Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido (1R*, 2R*)-2-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fenil-etanol,

2-{2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-etanol,

{1-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclopentil}-metanol,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2,5,6-trifluoro-benzoico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-propil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclobutil-amina,

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3-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-azepan-2-ona,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclopentil-amina,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-cicloheptil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-3-metil-butan-1-ol,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-metil-propan-1-ol,

terc-Butil-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-isopropil-amina,

Ácido 4-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(1-etil-propil)-amina,

4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,2-diamina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-fluoro-fenil)-amina,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,4-diamina,

(1R*, 2S*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-trifluorometil-fenil)-amina,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

(1-Aza-biciclo[2.2.2]oct-3-il)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

(R)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-fluoro-fenil)-amina,

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(3-Cloro-fenil)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ácido {3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-acético,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzamida,

Biciclo[2.2.1]hept-2-il-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

(1R*, 2R*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

5-(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-2-metoxi-fenol,

Ácido 3-(5-ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-4-hidroxi-benzoico,

(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-(3-metanosulfonil-fenil)-amina,

(1R*,2R*)-2-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ciclohexil-[5-(2,4-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

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[5-(2-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[3-metil-5-(4-trifluorometil-fenil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-piridin-4-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[5-(3-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

Ciclohexil-[5-(3-metoxi-4-nitro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2,4-Dicloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Ciclohexil-(3-metil-5-tiofen-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[5-(3,5-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

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Ciclohexil-[5-(2-etil-5-metil-2H-pirazol-3-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Cloro-2,6-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-(5-isoxazol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[3-metil-5-(5-piridin-2-il-tiofen-2-il)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-6-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

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2-Cloro-5-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dietilamino-etil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-propil)-N-etil-bencenosulfonamida,

Metil éster del ácido [5-(4-Cloro-fenil)-2-ciclohexilimino-[1,3,4]tiadiazol-3-il]-acético,

Metil éster del ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-hidroxi-etil)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2-diol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,6-dimetoxi-fenol,

6-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-piridin-2-ol,

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5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2,3-triol,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinolin-8-ol,

Ciclohexil-(3-metil-5-pirazin-2-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

5-[(E)-2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-vinil]-2-metoxi-fenol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol,

Ciclohexil-(3-metil-5-quinolin-8-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

4-(5-Ciclohexilimino-4-methyl-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

[5-(5-Cloro-1H-indol-2-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina; compuesto con ácido trifluoro-metanesulfónico,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfóhico,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

Ciclohexil-[5-(3,4-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Bromo-4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[5-(4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-fenil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-hidroxi-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Sal de clorhidrato de 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-*N*-(2H-tetrazol-5-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

Ciclohexil-{5-[4-(1-etil-1H-tetrazol-5-il)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isobutil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-N-metil-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-1-(3-hidroximetil-piperidin-1-il)-metanona,

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terc-Butil éster del ácido 2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido 2-({1-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-metanoil}-amino)-3-(4-hidroxi-fenil)-propiónico, compuesto con ácido 2,2,2-trifluoro-acético,

terc-Butil éster del ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido (S)-2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-piridin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-[4-(4-fluoro-fenil)-piperazin-1-il]-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-pirimidin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-metil-piperazin-1-il)-metanona,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(1-etil-pirrolidin-2-ilmetil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-Bencil-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-1)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

[5-(4-((N-ciano-N'-etilmorfolin)-carboximidamido)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

Ciclohexil-(3-metil-5-piridin-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

(5-Benzo[1,3]dioxol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-ciclohexil-amina,

Ciclohexil-[3-metil-5-(3,4,5-trimetoxi-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

Ácido 5-[5-(4-Ciano-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(cis-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[4-Metil-5-(trans-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

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4-[5-((1R*, 2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

(1R*, 3R*))-3-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ácido 4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-morfolin-4-il-etil)-benzamida,

Ácido 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

N-terc-Butil-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

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N-(1,1-dimetil-3-oxo-butil)-4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(2-Ciano-1,2,2-trimetil-etil)-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Metil éster del ácido 1-{4-[5-((1R*,3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoilamino}-ciclopropanocarboxílico,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-benzamida,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Ácido 5-[5-(4-Carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

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4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[4-Metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3,3-Difluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Fluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

(1R*,3R*)-3-{3-Metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-ilidenamino}-ciclohexanol,

Ácido 3-[5-(4-cloro-fenyl)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

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Ácido 3-[5-(4-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 2-fluoro-5-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-piperidin-1-il amina,

[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(tetrahidro-piran-4-il)-amina,

Ácido 3-[5-(4-acetilamino-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

N-{4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{5-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-piridin-2-il}-acetamida,

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3-[5-(4-Cloro-fenil)-3-metil-3H/-[1,3,4]tiadiazol-2-ilidenamino]-benzonitrilo,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-N-hidroxi-benzamidina,

3-{3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-metil-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzonitrilo,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzamida,

[5-(4-Bromo-3-metoxi-fenil)-3-metil-2,3-dihidro-[1,3,4]tiadiazol-2-il]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-hidroxi-benzamida,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-nitro-benzoico,

Metil éster del ácido 2-amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Metil éster del ácido 2-acetilamino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-1H-quinazolin-2,4-diona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

Metil éster del ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[3-metil-5-piridin-2-il-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-Cloro-3-sulfamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-{3-metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-iliden}-amina,

Ciclohexil-[3-metil-5-(4-nitro-fenil)-3H-[1,3,4] tiadiazol-2-iliden]-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenilamina,

[5-(4-(N-ciano-N'-(2-dimetilaminoetil)-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida,

[5-(4-(bis-etilsulfonilamino)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(1-(2-dimetilaminoetil)amino-2-nitro-vinilamino)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

(E)-N^1-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-2-nitro-eten-1,1-diamina,

[5-(*N*-ciano-*N'*-metil-4-carboximidamido-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

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[5-(4-(N-ciano-N'-amino-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-amida del ácido etanosulfónico,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-fenil]-urea,

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Metil éster del ácido 2-cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Metil éster del ácido 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzoico y

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzamida

15. Un compuesto de acuerdo con la reivindicación 14, seleccionado del grupo formado por:

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

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2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

terc-butil éster del ácido 2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

metil éster del ácido 2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

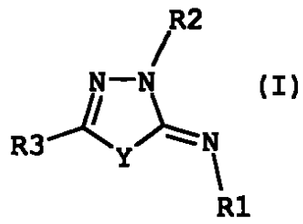
7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida, y

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea.

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16. Una composición farmacéutica que comprende un compuesto de la fórmula (I)



(I)

en donde:

- Y es O o S;

- R_1 es:

alquilo de C_1-C_{10},

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y

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- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o

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diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es $X_2-R'_3$ en donde:
- X_2 es un solo enlace o,

un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17},

idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo heterocíclico divalente, y

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, bioisóstero de ácido carboxílico, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

en donde,

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenilo de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-N(R_{19})-R_{18}

en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policiclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos optativamente se sustituyen con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o X_5-N(R_{19})-R_{18} en donde X_5 es un solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

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junto con un portador farmacéuticamente aceptable,

con la condición de que el compuesto de la fórmula (I) no sea etil éster del ácido 4-[2-Formilimino-5-(4-metoxi-fenil)-[1,3,4] tiadiazol-3-il]-butírico, o

etil éster del ácido 4-[5-(4-cloro-fenil)-2-formilimino-[1,3,4]tiadiazol-3-il]-butírico.

17. Una composición farmacéutica de acuerdo con la reivindicación 16, que comprende un compuesto de la fórmula (I), en donde R_1, R_2, R_3 e Y son lo definico en la reivindicación 18, con la condición de que cuando R_1 es C(=O)-H, R_2 no represente $(CH_2)_3$-$C(=O)OCH_2CH_3$.

18. Una composición farmacéutica que comprende un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, junto con un portador farmacéuticamente aceptable.

19. Una composición farmacéutica de acuerdo con la reivindicación 16, 17 o 18, para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante.

20. Un método para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante, que

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comprende administrar a un mamífero, particularmente a un humano, que lo necesita, una cantidad eficaz de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15.

21. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se debe tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

22. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

24. El uso de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, para la fabricación de

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un medicamento para el tratamiento de enfermedades para las cuales el tratamiento con un inhibidor de PDE7 es relevante.

24. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

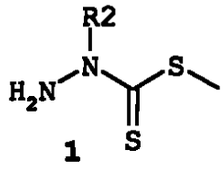
25. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

26. Un compuesto de la fórmula (I), definido en cualquiera de las reivindicaciones 1 a 15, como medicamento.

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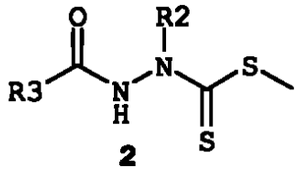
27. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reividindicación 1, con disulfuro de carbono y MeX donde X es un grupo saliente para obtener un compuesto de la fórmula 1



1

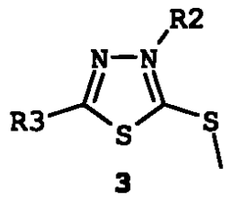
(b) reacción del S-metilditiocarbazato 1 con un cloruro de acilo R_3COCl en donde R_3 es lo definido en la reivindicación 1 para obtener un metilditiocarbazato acilado 2



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(c) ciclación del metilditiocarbazato acilado 2 en un 1,3,4-tiadiazol 3

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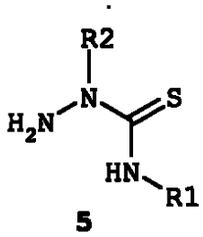
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(d) reacción del 1,3,4-tiadiazol 3 con una amina R_1NH_2 en donde R_1 es lo definido en reivindicación 1, para obtener el compuesto de la fórmula (I) en donde Y es S,

(e) aislación del compuesto de la fórmula (I).

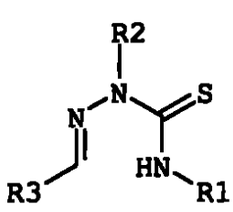
28. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$ en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5



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(b) reacción de la tiosemicarbazida 5 con un aldehído R_3CHO



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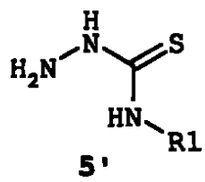
en donde R_3 es lo definido en la reivindicación 1, para obtener la tiosemicarbazona 6

(c) ciclación de la tiosemicarbazona 6 en el compuesto de la fórmula (I) en donde Y es S,

(d) aislación del compuesto de la fórmula (I).

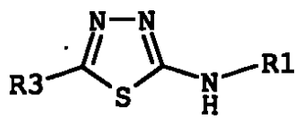
29. El proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de un ácido carboxílico R_3COOH en donde R_3 es lo definido en reivindicación 1, con la siguiente tiosemicarbazida 5'



5'

para obtener el 1,3,4-tiadiazol 7



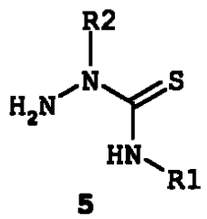
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(b) reacción del 1,3,4-tiadiazol 7 con R_2X, en donde R_2 es lo definido en la reivindicación 1 y X es un grupo saliente para obtener el compuesto de la fórmula (I) en donde Y es S

(c) aislación del compuesto de la fórmula (I).

30. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 14, que comprende los siguientes pasos:

(a) reacción de un ácido carboxílico R_3COOH, en donde R_3 es lo definido en la reivindicación 1, con la siguiente tiosemicarbazida 5



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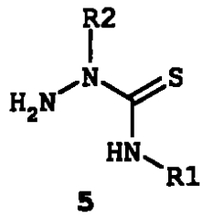
para obtener el compuesto final de la fórmula I en donde Y es S,

(b) aislación del compuesto de la fórmula (I).

31. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 11 o 13, en donde Y es S, que comprende los siguientes pasos:

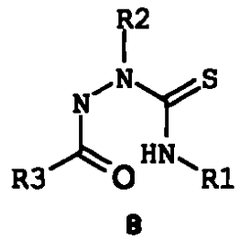
01046 1026

(a) reacción de una hidrazina sustituida R_2NHNH_2, en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$, en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5,



5

(b) reacción de la tiosemicarbazida 5 con R_3-C(=O)Cl, en donde R_3 es lo definido en la reivindicación 1, para formar la tiosemicarbazida 8 deseada



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(c) ciclación de la tiosemicarbazida 8 en el compuesto final de la fórmula I en donde Y es O,

(d) aislación del compuesto de la fórmula (I).

PATENT COOPERATION TREATY

RECEIVED ON
16.OCT.2001
Patent Fresnes
PCT

8/10 450
1027

From the RECEIVING OFFICE

To:
Hirsch, Denise
WARNER-LAMBERT COMPANY/Parke-Davis
Pfizer Global Res.& Development
Fresnes Laboratories
3-9, rue de la Loge, B.P. 100
F-94265 FRESNES
FRANCE

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing *(day/month/year)*	10.10.01
Applicant's or agent's file reference: 018315-A305 (018155)	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 01/ 11330	01/10/2001	02/10/2000

Applicant: WARNER-LAMBERT COMPANY

Title of the invention:

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.
3. ☐ Other:

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(g)).

Name and mailing address of the Receiving Office	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	M. DAVIDSON

Form PCT/RO/105 (Juli 1992)

PCT REQUEST

018315-A305

Original (for SUBMISSION) - printed on 28.09.2001 09:07:32 AM

0	For receiving Office use only	
0-1	International Application No.	PCT/EP 0 1 / 1 1 3 3 0
0-2	International Filing Date	0 1 OCT 2001 (0 1 10. 2001)
0-3	Name of receiving Office and "PCT International Application"	EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.03.2001)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	018315-A305
I	Title of invention	NEW THIADIAZOLES AND OXADIAZOLES AND THEIR USE AS PHOSPHODIESTERASE-7 INHIBITORS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	WARNER-LAMBERT COMPANY
II-5	Address:	201 Tabor Road Morris Plains, NJ 07950 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	1 973 385 2577
II-9	Facsimile No.	1 973 385 5533
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	VERGNE, Fabrice
III-1-5	Address:	1, allée du champ de la mare F-91190 GIF SUR YVETTE France
III-1-6	State of nationality	FR
III-1-7	State of residence	FR

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	DUCROT, Pierre
III-2-5	Address:	6 résidence d'Amblainvilliers F-91370 VERRIERES LE BUISSON France
III-2-6	State of nationality	FR
III-2-7	State of residence	FR
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	ANDRIANJARA, Charles
III-3-5	Address:	3 rue Auguste Daix F-94260 FRESNES France
III-3-6	State of nationality	FR
III-3-7	State of residence	FR
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	BERNARDELLI, Patrick
III-4-5	Address:	146 rue Boucicaut F-92260 FONTENAY AUX ROSES France
III-4-6	State of nationality	FR
III-4-7	State of residence	FR
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	LORTHIOIS, Edwige
III-5-5	Address:	6 rue de la Briquetterie F-75014 PARIS France
III-5-6	State of nationality	FR
III-5-7	State of residence	FR

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	HIRSCH, Denise
IV-1-2	Address:	WARNER-LAMBERT COMPANY c/o PARKE-DAVIS Pfizer Global Research & Development Fresnes Laboratories 3-9 rue de la Loge B.P. 100 F-94265 FRESNES France
IV-1-3	Telephone No.	33 1 40 96 32 00
IV-1-4	Facsimile No.	33 1 40 96 76 90
IV-1-5	e-mail	denise.hirsch@pfizer.com
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier regional application	
VI-1-1	Filing date	02 October 2000 (02.10.2000)
VI-1-2	Number	00402710.8
VI-1-3	Regional Office	EP
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)
VII-2	Request to use results of earlier search; reference to that search	
VII-2-1	Date	02 October 2000 (02.10.2000)
VII-2-2	Number	00402710.8
VII-2-3	Country (or regional Office)	EP

VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	1	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	5	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	1	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name:	in relation to this international application Warner-Lambert Company is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1 (ii)		Warner-Lambert Company is entitled as employer of the inventor, VERGNE, Fabrice
VIII-2-1 (ii)		Warner-Lambert Company is entitled as employer of the inventor, DUCROT, Pierre
VIII-2-1 (ii)		Warner-Lambert Company is entitled as employer of the inventor, ANDRIANJARA, Charles
VIII-2-1 (ii)		Warner-Lambert Company is entitled as employer of the inventor, BERNARDELLI, Patrick
VIII-2-1 (ii)		Warner-Lambert Company is entitled as employer of the inventor, LORTHIOIS, Edwige
VIII-2-1 (iv)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)): Name:	in relation to this international application VERGNE, Fabrice is entitled to claim priority of earlier application No. 00402710.8 by virtue of the following:
VIII-3-1 (i)		the applicant is the inventor of the subject matter for which protection was sought by way of the earlier application
VIII-3-1 (ix)	This declaration is made for the purposes of:	US

VIII-3-2	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(ii) and 51bis.1(a)(ii)): Name:	in relation to this international application DUCROT, Pierre is entitled to claim priority of earlier application No. 00402710.8 by virtue of the following:
VIII-3-2 (i)		the applicant is the inventor of the subject matter for which protection was sought by way of the earlier application
VIII-3-2 (k)	This declaration is made for the purposes of:	US

VIII-3-3	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)): Name:	in relation to this international application ANDRIANJARA, Charles is entitled to claim priority of earlier application No. 00402710.8 by virtue of the following:
VIII-3-3 (i)		the applicant is the inventor of the subject matter for which protection was sought by way of the earlier application
VIII-3-3 (ix)	This declaration is made for the purposes of:	US

VIII-3-4	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)): Name:	in relation to this international application BERNARDELLI, Patrick is entitled to claim priority of earlier application No. 00402710.8 by virtue of the following:
VIII-3-4 (i)		the applicant is the inventor of the subject matter for which protection was sought by way of the earlier applicati n
VIII-3-4 (b)	This declaration is made for the purposes of:	US

VIII-3-5	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)): Name:	in relation to this international application LORTHIOIS, Edwige is entitled to claim priority of earlier application No. 00402710.8 by virtue f the following:
VIII-3-5 (i)		the applicant is the inventor of the subject matter for which protection was sought by way of the earlier application
VIII-3-5 (ix)	This declaration is made for the purposes of:	US

VIII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to the international application of which it forms a part (if filing declaration with application). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States f America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	00402710.8, EP, 02 October 2000 (02.10.2000)

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name:	VERGNE, Fabrice
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	GIF SUR YVETTE, France
VIII-4-1-1-3	Mailing address:	1, allée du champ de la mare F-91190 GIF SUR YVETTE France
VIII-4-1-1-4	Citizenship:	FR
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	09/28/2001

VIII-4-1 -2-1	Name:	DUCROT, Pierre
VIII-4-1 -2-2	Residence: (city and either US State, if applicable, or country)	VERRIERES LE BUISSON, France
VIII-4-1 -2-3	Mailing address:	6 résidence d'Amblainvilliers F-91370 VERRIERES LE BUISSON France
VIII-4-1 -2-4	Citizenship:	FR
VIII-4-1 -2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	09/28/01
VIII-4-1 -2-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1 -3-1	Name:	ANDRIANJARA, Charles
VIII-4-1 -3-2	Residence: (city and either US State, if applicable, or country)	FRESNES, France
VIII-4-1 -3-3	Mailing address:	3 rue Auguste Daix F-94260 FRESNES France
VIII-4-1 -3-4	Citizenship:	FR
VIII-4-1 -3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -3-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	09/28/2001

VIII-4-1 -4-1	Name:	BERNARDELLI, Patrick
VIII-4-1 -4-2	Residence: (city and either US State, if applicable, or country)	FONTENAY AUX ROSES, France
VIII-4-1 -4-3	Mailing address:	146 rue Boucicaut F-92260 FONTENAY AUX ROSES France
VIII-4-1 -4-4	Citizenship:	FR
VIII-4-1 -4-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -4-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	09/28/01
VIII-4-1 -5-1	Name:	LORTHIOIS, Edwige
VIII-4-1 -5-2	Residence: (city and either US State, if applicable, or country)	PARIS, France
VIII-4-1 -5-3	Mailing address:	6 rue de la Briquetterie F-75014 PARIS France
VIII-4-1 -5-4	Citizenship:	FR
VIII-4-1 -5-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -5-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	09/28/01

PCT REQUEST

018315-A305

Original (for SUBMISSION) - printed on 28.09.2001 09:07:32 AM

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	15	–
IX-2	Description	200	–
IX-3	Claims	34	–
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	–
IX-7	TOTAL	250	
	Accompanying items	**paper document(s) attached**	**electronic file(s) attached**
IX-8	Fee calculation sheet	✓	–
IX-9	Original separate power of attorney	✓	–
IX-17	PCT-EASY diskette	–	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	HIRSCH, Denise	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	01.10.01	01 OCT 2001
10-2	Drawings:		
10-2-1	Received		
10-2-2	Not received		
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application		
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)		
10-5	International Searching Authority	ISA/EP	
10-6	Transmittal of search copy delayed until search fee is paid		

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

8/10.

01063

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

[en el margen superior derecho aparece un sello que reza:] Recibido el 16 de Oct de 2001. Patentes. Fresnes

PCT

Notificación del número de solicitud internacional y de la fecha de presentación internacional.

(Norma 20.5(c) del PCT)

De la OFICINA RECEPTORA

Para:

Hirsch, Denise

WARNER-LAMBERT COMPANY/Parke-Davis

Pfizer Global Res. & Development

Fresnes Laboratories

3-9, rue de la Loge, B.P. 100

F-94265 FRESNES

Francia

Fecha de envío *(día/mes/año)*: **10.10.01**

Referencia del agente o del solicitante: ~~**018315-A305**~~. [en letra manuscrita aparece lo siguiente:] 018155

NOTIFICACIÓN IMPORTANTE

Solicitud internacional No.: **PCT/EP 01/11330**

Solicitante: WARNER-LAMBERT COMPANY

0109 647

Título de la invención:

1. Por medio de la presente se notifica al solicitante que se ha otorgado a la solicitud internacional el número de solicitud internacional y fecha de presentación internacional indicado anteriormente.

2. También se notifica al solicitante que la copia de registro de la solicitud internacional ha sido remitida a la Oficina Internacional en la fecha de envío anteriormente indicada.

3. ☐ Otro:

*La Oficina Internacional controla la remisión de la copia de registro por parte de la Oficina Receptora y notificará al solicitante de su recepción (mediante el formulario PCT/IB/301) (Norma 22.1 (c)).

Nombre y domicilio para correspondencia de la Oficina Receptora

Oficina de Patentes Europea, P.B. 5818 Patentlaan 2

NL-2280 HV Rijswijk

Tel. (+31-70) 340-2040

Fax: (+31-70) 340-3016

1045

01063

Funcionario autorizado:

[firma ilegible]

M. DAVIDSON

1046

01062

PCT. PEDIDO 1/15 018315-A305

Original (para **PRESENTAR**)- impreso el 28.09.2001 09:07:32 AM

0 **0-1**	**Para uso exclusivo de la Oficina receptora** Solicitud Internacional No.	**PCT/EP 01/11330**
0-2	Fecha de Presentación Internacional	**01 OCT 2001 (01.10.2001)**
0-3	Nombre de la Oficina receptora y "Solicitud Internacional PCT"	**OFICINA DE PATENTES EUROPEA** **SOLICITUD INTERNACIONAL POR PCT**

0-4 0-4-1	**Formulario-PCT/RO/101 PCT** Pedido Preparado con	 **PCT-SIMPLE [del inglés *PCT-EASY*] Versión 2.92** **(actualizado el 01.03.2001)**
0-5	**Petición** El que suscribe solicita que la presente solicitud internacional siga el proceso de acuerdo con el Tratado de Cooperación en	

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01067

	materia de Patentes.	
0-6	**Oficina Receptora (especificada por el solicitante)**	**OFICINA DE PATENTES EUROPEA (EPO) (RO/EP)**
0-7	**Referencia de archivo del solicitante o del agente**	**018315-A305**
I	**Título de la invención**	**NUEVOS TIADIAZOLES Y OXADIAZOLES Y SU USO COMO INHIBIDORES DE FOSFODIESTERASA-7**
II	**Solicitante**	
II-1	Esta persona es:	**Solamente solicitante**
II-2	Solicitante para:	**Todos los estados designados excepto US**
II-4	Nombre:	**WARNER-LAMBERT COMPANY**
II-5	Domicilio:	**201 Tabor Road** **Morris Plains, NJ 7950** **Estados Unidos**
II-6	Nacionalidad	**US**
II-7	Residencia	**US**
II-8	No. de Teléfono:	**1 973 385 2577**
II-9	No. de Fax:	**1 973 385 5533**
III-1	**Solicitante y/o inventor**	

01068

III-1-1	Esta persona es:	**Solicitante e inventor**
III-1-2	Solicitante para	**US solamente**
III-1-4	Nombre (APELLIDO, Nombre)	**VERGNE, Fabrice**
III-1-5	Domicilio:	**1, allée du champ de la mare** **F-91190 GIF SUR YVETTE** **Francia**
III-1-6	Nacionalidad	**FR**
III-1-7	Residencia	**FR**

III-2	**Solicitante y/o inventor**	
III-2-1	Esta persona es:	**Solicitante e inventor**
III-2-2	Solicitante para	**US solamente**
III-2-4	Nombre (APELLIDO, Nombre)	**DUCROT, Pierre**
III-2-5	Domicilio:	**6 résidence d´Amblainvilliers** **F-91370 VERRIERES LE BUISSON** **Francia**

1049

III-2-6	Nacionalidad	FR
III-2-7	Residencia	FR
III-3	**Solicitante y/o inventor**	
III-3-1	Esta persona es:	**Solicitante e inventor**
III-3-2	Solicitante para	**US solamente**
III-3-4	Nombre (APELLIDO, Nombre)	**ANDRIANJARA, Charles**
III-3-5	Domicilio:	**3 rue Auguste Daix** **F-94260 FRESNES** **Francia**
III-3-6	Nacionalidad	FR
III-3-7	Residencia	FR
III-4	**Solicitante y/o inventor**	
III-4-1	Esta persona es:	**Solicitante e inventor**

1050

III-4-2	Solicitante para	**US solamente**
III-4-4	Nombre (APELLIDO, Nombre)	**BERNARDELLI, Patrick**
III-4-5	Domicilio:	**146 rue Boucicaut** **F-92260 FONTENAY AUX ROSES** **Francia**
III-4-6	Nacionalidad	FR
III-4-7	Residencia	FR
III-5	**Solicitante y/o inventor**	
III-5-1	Esta persona es:	**Solicitante e inventor**
III-5-2	Solicitante para	**US solamente**
III-5-4	Nombre (APELLIDO, Nombre)	**LORTHIOIS, Edwige**
III-5-5	Domicilio:	**6 rue de la Briquetterie** **F-75014 PARIS** **Francia**
III-5-6	Nacionalidad	**FR**

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III-5-7	Residencia	**FR**

IV-1	**Agente o representante; o domicilio para correspondencia** La persona identificada a continuación ha sido designada/es designada por la presente para que actúe en nombre del(os) solicitante(s) ante las Autoridades Internacionales competentes, como:	**agente**
IV-1-1	Nombre (APELLIDO, nombre)	**HIRSCH, Denise**

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010/12

IV-1-2	Domicilio:	WARNER-LAMBERT COMPANY c/o Parke-Davis Pfizer Global Research & Development Fresnes Laboratories 3-9, rue de la Loge, B.P. 100 F-94265 FRESNES Francia
IV-1-3	No. Teléfono:	**33 1 40 96 32 00**
IV-1-4	No. Fax:	**33 1 40 96 76 90**
IV-1-5	e-mail	**denise.hirsch@pfizer.com**
V	**Designación de estados**	
V-1	Patente Regional (seguido de cada designación correspondiente se indica entre paréntesis si tiene algún otro tipo de protección o tratamiento)	**AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW y cualquier otro estado firmante del Protocolo de Harare y del PCT** **EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro estado firmante de la Convención de Patentes Euroasiática y del PCT**

		EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR y cualquier otro estado firmante de la Convención de Patentes Europea y del PCT **OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier tr estado miembro de la OAPI y firmante del PCT**
V-2	Patente nacional (seguido de cada designación correspondiente se indica entre paréntesis si tiene algún otro tipo de protección o tratamiento)	**AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW**

(85)
010/14

V-5	**Declaración Precautoria sobre Designaciones:** Además de las designaciones efectuadas en los puntos V-1, V-2 y V-3, el solicitante también efectúa conforme a la Norma 4.9(b) todas las designaciones que están permitidas conforme al PCT salvo la(s) designación(es) indicadas en el punto V-6 que figura a continuación. El solicitante declara que aquellas designaciones adicionales están sujetas a confirmación y que cualquier designación que no se confirme con anterioridad al vencimiento de los 15	

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	anterioridad al vencimiento de los 15 meses desde la fecha de prioridad se considerará desistida por el solicitante al vencimiento de dicho plazo	
V-6	**Exclusión(es) de las designaciones precautorias**	**NINGUNA**
VI-1	**Reivindicación de prioridad de una solicitud regional anterior**	
VI-1-1	Fecha de presentación	**02 de Octubre de 2000 (02.10.2000)**
VI-1-2	Número	**00402710.8**
VI-1-3	Oficina Regional	**EP**

010/6 P56

VI-2	**Pedido de documento de prioridad** Se solicita a la Oficina receptora que prepare y envíe a la Oficina Internacional una copia certificada de la(s) solicitud(es) anterior(es) que se identificó con el/los punto(s):	**VI-1**	
VII-1	**Autoridad de Búsqueda Internacional elegida**	**Oficina de Patentes Europea (EPO) (ISA/EP)**	
VII-2	**Pedido para hacer uso de los resultados de una búsqueda anterior; referencia a dicha búsqueda**		
VII-2-1	Fecha	02 de Octubre de 2000 (02.10.2000)	
VII-2-2	Número	00402710.8	
VII-2-3	País (u Oficina regional)	EP	

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VIII	Declaraciones	Número de declaraciones	0107
VIII-1	Declaración sobre la identidad del inventor	-	
VIII-2	Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a solicitar una patente y que ésta le sea otorgada	1	
VIII-3	Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a reivindicar la prioridad de la solicitud anterior	5	
VIII-4	Declaración de inventor (sólo para los fines de los Estados Unidos)	1	

01078 153

VIII-5	Declaración sobre revelaciones no perjudiciales o excepciones a la falta de novedad	-	

Original (para **PRESENTAR**)- impreso el 28.09.2001 09:07:32 AM

VIII-2-1	**Declaración: derecho a solicitar una patente y que ésta sea otorgada**: Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a solicitar una patente y que ésta le sea otorgada (Normas 4.17(ii) y 51bis.1 (a)(ii), en caso en que la declaración conforme a la Norma 4.17(iv) no sea adecuada:	con relación a esta solicitud internacional

010/3 1059

	Nombre:	Warner Lambert Company tiene derecho a solicitar una patente y que ésta le sea otorgada en virtud de lo siguiente:
VIII-2-1 (ii)		Warner Lambert Company tiene derecho como empleador del inventor, VERGNE, Fabrice
VIII-2-1 (ii)		Warner Lambert Company tiene derecho como empleador del inventor, DUCROT, Pierre
VIII-2-1 (ii)		Warner Lambert Company tiene derecho como empleador del inventor, ANDRIANJARA, Charles
VIII-2-1 (ii)		Warner Lambert Company tiene derecho como empleador del inventor, BERNARDELLI, Patrick

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VIII-2-1 (ii)		Warner Lambert Company tiene derecho como empleador del inventor, LORTHIOIS
VIII-2-1 (ix)	Esta declaración se efectúa para los fines de:	Todas las designaciones salvo la designación de Estados Unidos

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VIII-3-1	**Declaración: derecho a reivindicar prioridad:** Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a reivindicar prioridad de la solicitud anterior que se identifica a continuación, si el solicitante que presentó la solicitud anterior o se el nombre del solicitante cambió desde el momento de la presentación de la solicitud anterior (Normas 4.17(ii) y 51bis.1 (a)(ii) Nombre:	con relación a esta solicitud internacional VERGNE, Fabrice Tiene derecho a reivindicar prioridad de la solicitud anterior No. 0402710.8 e virtud de lo siguiente:
VIII-3-1 (i)		el solicitante es el inventor del objeto que se desea proteger por medio de la solicitud anterior

1062

010/82

VIII- 3-1 (iX)	Esta declaración se hace para los fines de:	US	

Original (para **PRESENTAR**)- impreso el 28.09.2001 09:07:32 AM

VIII- **3-2**	**Declaración: derecho a reivindicar prioridad:** Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a reivindicar prioridad de la solicitud anterior que se identifica a continuación, si el solicitante que presentó la solicitud anterior o se el nombre del solicitante cambió desde el momento de la presentación de la solicitud anterior (Normas 4.17(ii) y 51bis.1 (a)(ii)	con relación a esta solicitud internacional

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01/03

	Nombre:	DUCROT, Pierre tiene derecho a reivindicar prioridad de la solicitud anterior No. 0402710.8 e virtud de lo siguiente:	
VIII-3-2(i)		el solicitante es el inventor del objeto que se desea proteger por medio de la solicitud anterior	
VIII-3-2 (iX)	Esta declaración se hace para los fines de:	US	

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VIII-3-3	**Declaración: derecho a reivindicar prioridad:** Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a reivindicar prioridad de la solicitud anterior que se identifica a continuación, si el solicitante que presentó la solicitud anterior o se el nombre del solicitante cambió desde el momento de la presentación de la solicitud anterior (Normas 4.17(ii) y 51bis.1 (a)(ii)	con relación a esta solicitud internacional
	Nombre:	ANDRIANJARA, Charles tiene derecho a reivindicar prioridad de la solicitud anterior No. 0402710.8 e virtud de lo siguiente:
VIII-3-3(i)		el solicitante es el inventor del objeto que se desea proteger por medio de la solicitud anterior

01035 1065

VIII-3-3 (iX)	Esta declaración se hace para los fines de:	US	

018315-A305

Original (para **PRESENTAR**)- impreso el 28.09.2001 09:07:32 AM

VIII-3-4	**Declaración: derecho a reivindicar prioridad:** Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a reivindicar prioridad de la solicitud anterior que se identifica a continuación, si el solicitante que presentó la solicitud anterior o se el nombre del solicitante cambió desde el momento de la presentación de la solicitud anterior (Normas 4.17(ii) y 51bis.1 (a)(ii)	con relación a esta solicitud internacional

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	Nombre:	BERNARDELLI, Patrick tiene derecho a reivindicar prioridad de la solicitud anterior No. 0402710.8 e virtud de lo siguiente:	
VIII-3-4(i)		el solicitante es el inventor del objeto que se desea proteger por medio de la solicitud anterior	
VIII-3-4 (iX)	Esta declaración se hace para los fines de:	US	

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VIII-3-5	**Declaración: derecho a reivindicar prioridad:** Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a reivindicar prioridad de la solicitud anterior que se identifica a continuación, si el solicitante que presentó la solicitud anterior o se el nombre del solicitante cambió desde el momento de la presentación de la solicitud anterior (Normas 4.17(ii) y 51bis.1 (a)(ii) Nombre:	con relación a esta solicitud internacional LORTHIOIS, Edwige tiene derecho a reivindicar prioridad de la solicitud anterior No. 0402710.8 e virtud de lo siguiente:
VIII-3-5(i)		el solicitante es el inventor del objeto que se desea proteger por medio de la solicitud anterior

(106) 1068

VIII-3-5 (iX)	Esta declaración se hace para los fines de:	US	

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VIII-4-1	**Declaración: Inventor (sólo para los fines de la designación de Estados Unidos)** Declaración de inventor (Normas 4.17 (iv) y 51bis.1 (a)(iv)) para los fines de la designación de Estados Unidos:	Por medio de la presente declaro que soy el verdadero, primero y único (si a continuación sólo aparece un inventor) o co-inventor (si a continuación aparece más de un inventor) del objeto que desea protegerse. Esta declaración se dirige a la solicitud internacional de la que forma parte (si la declaración se presenta junto con la solicitud). Por la presente declaro que mi residencia, domicilio para correspondencia, y ciudadanía son las que figuran al lado de mi nombre. Por la presente declaro que he revisado y comprendido +

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		los contenidos de la solicitud internacional identificada anteriormente, incluso las reivindicaciones de tal solicitud. He identificado en el pedido de dicha solicitud, conforme con la Norma 4.10 del PCT, toda reivindicación para prioridad extranjera, y he identificado a continuación, bajo el título "solicitudes anteriores", por medio del número de solicitud, país o Miembro de la Organización Mundial de Comercio, día, mes, y año de presentación, toda solicitud para un certificado de inventor o patente presentada en otro país que no sea Estados Unidos

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		Unidos, incluso toda solicitud internacional por PCT que designe por lo menos un país que no sea Estados Unidos, con una fecha de presentación anterior a la de la solicitud sobre la cual se reivindica prioridad extranjera.
VIII-4-1-1	Solicitudes anteriores:	00402710.8, EP, 02 de Octubre de 2000 (02.10.2000)

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		Por la presente reconozco el deber de revelar información de la que tengo conocimiento que es material de patentabilidad como lo define el 37 C.F.R. §1.56, incluso para continuaciones en parte, información material que estuvo disponible entre la fecha de presentación de la solicitud anterior y la fecha de presentación internacional de la continuación en parte. Por la presente declaro que todas las declaraciones aquí efectuadas y de propio conocimiento son verdaderas y que todas las declaraciones efectuadas sobre la información y la opinión son tomadas por verfd

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		verdaderas; y además que estas declaraciones se efectuaron sabiendo que las declaraciones falsas y deliberadas y similares están penadas con prisión o con la aplicación de una multa, o ambas, conforme el Artículo 1001 del Título 18 del Código de los Estados Unidos y que estas declaraciones falsas y deliberadas pueden poner en peligro la validez de la solicitud internacional o cualquier patente concedida a partir de ésta.
VIII-4-1-1-1	Nombre:	VERGNE, Fabrice
VIII-4-1-1-2	Residencia: (ciudad y Estado de US, si corresponde, o país)	GIF SUR YVETTE, Francia

01094/024

VIII-4-1-1-3	Domicilio para correspondencia:	1, allée du champ de la mare F-91190 GIF SUR YVETTE Francia
VIII-4-1-1-4	Ciudadanía	FR
VIII-4-1-1-5	Firma del inventor: (si no figura en el pedido, o si la declaración está corregida o se agregó conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional. La firma debe ser aquella del inventor, no la del agente)	[firma ilegible]
VIII-4-1-1-6	Fecha: (de la firma que no estaba en el pedido, o de la declaración que se corrige o se agrega conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional)	28/09/2001

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Original (para **PRESENTAR**)- impreso el 28.09.2001 09:07:32 AM

VIII-4-1-2-1	Nombre:	DUCROT, Pierre
VIII-4-1-2-2	Residencia: (ciudad y Estado de US, si corresponde, o país)	VERRIERES LE BUISSON, Francia
VIII-4-1-2-3	Domicilio para correspondencia:	6 résidence d'Amblainvilliers F-91370 VERRIERES LE BUISSON Francia
VIII-4-1-2-4	Ciudadanía	FR

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VIII-4-1-2-5	Firma del inventor: (si no figura en el pedido, o si la declaración está corregida o se agregó conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional. La firma debe ser aquella del inventor, no la del agente)	[firma ilegible]
VIII-4-1-2-6	Fecha: (de la firma que no estaba en el pedido, o de la declaración que se corrige o se agrega conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional)	28/09/2001
VIII-4-1-3-1	Nombre:	ANDRIANJARA, Charles
VIII-4-1-3-2	Residencia: (ciudad y Estado de US, si corresponde, o país)	FRESNES, Francia

VIII-4-1-3-3	Domicilio para correspondencia:	3 rue Auguste Daix F-94260 FRESNES Francia
VIII-4-1-3-4	Ciudadanía	FR
VIII-4-1-3-5	Firma del inventor: (si no figura en el pedido, o si la declaración está corregida o se agregó conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional. La firma debe ser aquella del inventor, no la del agente)	[firma ilegible]
VIII-4-1-3-6	Fecha: (de la firma que no estaba en el pedido, o de la declaración que se corrige o se agrega conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional)	28/09/2001

Original (para **PRESENTAR**)- impreso el 28.09.2001 09:07:32 AM

VIII-4-1-4-1	Nombre:	BERNARDELLI, Patrick
VIII-4-1-4-2	Residencia: (ciudad y Estado de US, si corresponde, o país)	FONTENAY AUX ROSES, Francia
VIII-4-1-4-3	Domicilio para correspondencia:	14 rue Boucicaut F-92260 FONTENAY AUX ROSES Francia
VIII-4-1-4-4	Ciudadanía	FR

01093 1079

VIII-4-1-4-5	Firma del inventor: (si no figura en el pedido, o si la declaración está corregida o se agregó conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional. La firma debe ser aquella del inventor, no la del agente)	[firma ilegible]
VIII-4-1-4-6	Fecha: (de la firma que no estaba en el pedido, o de la declaración que se corrige o se agrega conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional)	28/09/2001
VIII-4-1-5-1	Nombre:	LORTHIOIS, Edwige
VIII-4-1-5-2	Residencia: (ciudad y Estado de US, si corresponde, o país)	PARIS, Francia

VIII-4-1-5-3	Domicilio para correspondencia:	6 rue de la Briquetterie F-75014 PARIS Francia
VIII-4-1-5-4	Ciudadanía	FR
VIII-4-1-5-5	Firma del inventor: (si no figura en el pedido, o si la declaración está corregida o se agregó conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional. La firma debe ser aquella del inventor, no la del agente)	[firma ilegible]
VIII-4-1-5-6	Fecha: (de la firma que no estaba en el pedido, o de la declaración que se corrige o se agrega conforme a la Norma 26ter con posterioridad a la presentación de la solicitud internacional)	28/09/2001

Original (para **PRESENTAR**)- impreso el 28.09.2001 09:07:32 AM

IX	**Lista de verificación**	Número de páginas	Archivo(s) electrónico(s) adjunto(s)
IX-1	Pedido (con páginas de la declaración)	**15**	-
IX-2	Memoria descriptiva	**200**	-
IX-3	Reivindicaciones	**34**	-
IX-4	Resumen	**1**	**EZABST00.TXT**
IX-5	Dibujos	**0**	-
IX-7	TOTAL	**250**	
	Items que se acompañan	Documento(s) en papel adjunto(s)	Archivo(s) electrónico(s) adjunto(s)
IX-8	Planilla de cálculo de aranceles	✓	-
IX-9	Poder General original por separado	✓	-
IX-17	Diskette de PCT-SIMPLE	-	**Diskette**

01102 1032

IX-19	**Figura que debe acompañar al resumen**	
IX-20	**Idioma de presentación de la solicitud internacional**	**Inglés**
X-1	**Firma del solicitante, agente o representante**	[firma ilegible]
X-1-1	Nombre (APELLIDO, nombre)	**HIRSCH, Denise**

PARA USO EXCLUSIVO DE LA OFICINA RECEPTORA

10-1	**Fecha real de recepción de la solicitud internacional**	(01.10.01)	01 OCT 2001
10-2 10-2-1 10-2-2	**Dibujos** Recibidos No recibidos		
10-3	**Fecha corregida de recepción efectiva debido a la recepción posterior pero en plazo de documentos o dibujos que completan la solicitud internacional**		

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10-4	Fecha de recepción en plazo de las correcciones solicitadas conforme al Artículo 11(2) del PCT:	
10-5	Autoridad de Búsqueda Internacional	ISA/EP
10-6	Envío de copia de búsqueda demorada hasta que se efectúe el pago del arancel de búsqueda	
PARA USO EXCLUSIVO DE LA OFICINA INTERNACIONAL		
11-1	Fecha de recepción de la copia de registro por la Oficina internacional	

Legal Division, Patents Dept.
Pfizer
3-9, rue de la Loge – BP 100
F-94265 Fresnes Cedex
Tél. : 01 40 96 32 31 ou 01 40 96 76 97
Fax : 01 40 96 76 90

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EUROPEAN PATENT OFFICE
P.B. 5818
PATENTLAAN2
NL-2280 HV RIJSWIJK (ZH)
THE NETHERLANDS

December 5th, 2002

Fax: +31 70 340 3016
& mail confirmation

Our ref.: 018155 (A-305)
DH/MB

Re: International application No. PCT/EP01/11330
Applicant : Warner-Lambert Company

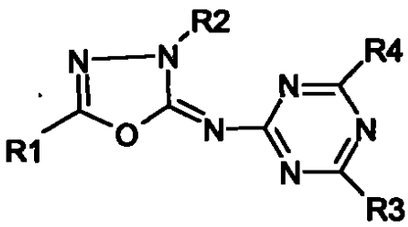
Dear Sir,

This is in response to the second written opinion relative to the subject application. Please find enclosed two sets of amended claims, one of which comprising underlined amendments. The amendments are detailed below.

The examiner has considered that claims 1-5, 7-9, 13 and 31 lack novelty in view of D1.

D1: DD251979 (1987)

D1 discloses compounds of formula



wherein R1 and R2 are selected from alkyl or aryl and R3 and R4 are selected from alkoxy, aryloxy, alkylthio, arylthio, alkylamino, arylamino, dialkylamino, diarylamino, alkylarylamino, optionally substituted hydrazine or OH, Cl.

In order to overcome the examiner's objection, the following disclaimer has been added in claim 1:

"When R3 represents a phenyl or a cycloalkyl, unsubstituted or substituted, and Y represents O, then R1 is other than substituted 1,3,5-triazine"

The above amendments should overcome the objection raised by the examiner.

Sincerely yours,

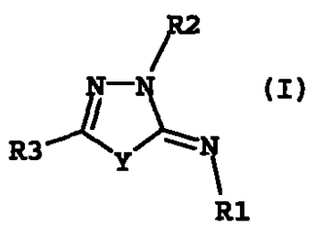
Denise Hirsch
European Patent Attorney

Encl.: 2 sets of claims.

01106

CLAIMS

1. A compound having the following formula (I),



(I)

in which

- Y is O or S;
- R1 is:
  - C_4-C_{10} alkyl,
  - C_2-C_{10} alkenyl,
  - C_2-C_{10} alkynyl,
  - cycloalkyl,
  - cycloalkenyl,
  - heterocycle,
  - aryl,
  - or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are

selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_4-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
2) $COOR_5$, OR_5, SO_2R_5,
3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
    2) OR_5, $=NR_5$ or,
    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

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cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=N\text{-}SO_2NH_2)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$
  4) heterocycle optionally substituted with one or several groups R_5;

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl

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optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-$\underset{R_{19}}{N}$-R_{18} in which X_5 is a single bond or lower alkylene and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;

- X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21},or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-$\underset{R_{19}}{N}$-R_{18} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;

- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

with the proviso that,

- when R1 is phenyl, it bears at least one substituent other than H,

- when X_2 is a single bond and both R1 and R'_3 are phenyl, each of R1 and R'_3 bear at least one substituent other than H,

- when X_2 is a single bond and R'_3 is phenyl, R'_3 is not substituted by an ester or a carboxylic acid in the ortho position,

- When Y represents O and R3 represents a phenyl or a cycloalkyl, unsubstituted or substituted, then R1 is other than substituted 1,3,5-triazine,

- the atom of R3 which is linked to the thiadiazole group is a carbon atom,

with the exclusion of the following compounds,

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(3,5-diphenyl-3H-[1,3,4]oxadiazol-2-ylidene)-naphthalen-2-yl-amine,
tert-butyl-(3-*tert*-butyl-5-phenyl-3*H*-[1,3,4]oxadiazol-2-ylidene)-amine,
2-[(3-methyl-5-phenyl-3H-[1,3,4]oxadiazol-2-ylideneamino)-methylene]-malonic acid diethyl ester,
[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]phenyl-methanone,
(4-methoxy-phenyl)-[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-methanone,
[4-(4-fluoro-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl-methanone,
1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-methanone,
1-[4-Phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,
1-Phenyl-1-(4-phenyl-5-*p*-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,
Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethyl-cyclopent-1-enylmethyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
2-(3,5-Diphenyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,
2-[3-Phenyl-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,
2-[5-(1-Phenyl-methanoyl)-3-*p*-tolyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,
2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

2. A compound according to claim 1 in which R1, R2, R3 and Y are as defined in claim 1 with the proviso that, when R2 is a phenyl, unsubstituted or substituted whith 1 to 3 chorine or with a methyl, then R3 does not represent C(=O)-phenyl, C(=O)-thienyl, phenyl or CH_2-(2,3,3-trimethyl-cyclopent-1-enyl).

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3. A compound of formula (I) as defined in claim 1 or 2, in which R1 is:

C_4-C_6 alkyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:
  1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$,
  wherein R_5 is selected from hydrogen or lower alkyl, optionally substituted with OH, and R_6, R_9 and R_{10} are identical or different and are selected from hydrogen or lower alkyl.

4. A compound as defined in any one of claims 1 to 3 in which R2 is lower alkyl.

5. A compound as defined in any one of claims 1 to 4 in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, and,
- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,

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or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

6. A compound as defined in any one of claims 1 to 5, in which R1 is:

cycloalkyl, preferably cyclohexane,

cycloalkenyl,

aryl, preferably phenyl,

or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$.

  wherein R_5 and R_6 are identical or different and are selected from hydrogen or methyl.

7. A compound as defined in any one of claims 1 to 6, in which R2 is CH_3.

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8. A compound as defined in any one of claims 1 to 7 in which R3 is X_2-R'$_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or -CH_2-, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

9. A compound according to claims 3, 4 and 5.

10. A compound according to claims 6, 7 and 8.

11. A compound as defined in claim 1 in which R1 is:

cyclohexane,
phenyl
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:

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1) H, halogen, CF_3,
2) COOH, OH,
3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same or different and are selected from H or lower alkyl,

R2 is CH_3, and,

R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond, and,
- R_{17} is:
  1) CN, OH, CF_3, =O, C_1-C_6 alkoxy, halogen,
  2) $COOR_5$, SO_2R_5,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 or R_6,
  4) heterocycle optionally substituted with one or several groups R_5.

12. A compound as defined in any one of claims 1 to 11 in which Y is S.

13. A compound as defined in any one of claims 1 to 11 in which Y is O.

14. A compound selected from the group consisting of:
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4] thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,

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(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol,
2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol,
{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-propyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol,
tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-isopropyl-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,

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N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine,
(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine,
3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine,
(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide,
Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol,
3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid,

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid,
(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine,
(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[5-(3-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol,
compound with trifluoro-methanesulfonic acid
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,

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2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide,
[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol,
6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol,
Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol,
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-*N*-(2H-tetrazol-5-yl)-benzamide hydrochloride salt,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
2-({1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-methanoyl}-amino)-3-(4-hydroxy-phenyl)-propionic acid, compound with 2,2,2-trifluoro-acetic acid,

(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,
N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,

[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,

Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,

(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine,

Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

5-[5-(4-Cyano-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,

4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

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4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester,
4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

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4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
(1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,

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3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,

[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine,

[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine,

3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,

N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide,

3-[5-(4-Chloro-phenyl)-3-methyl-3H/-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile,

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine,

3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-methyl-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide,

[5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine,
[5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide,
[5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
(E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine,
[5-(*N*-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-urea,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester, and,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide.

15. A compound according to claim 14, selected from the group consisting of:

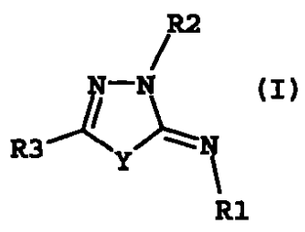
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-

[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-
yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-
benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-
benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-
benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-
phenyl)-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-
phenyl)-propionic acid; compound with 2,2,2-trifluoro-
acetic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-
benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-
propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,

N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide, and,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea.

16. Pharmaceutical composition comprising a compound of formula (I),



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wherein:

- Y is O or S;
- R1 is:

C_1-C_{10} alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a polycyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or a divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:

lower alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,

aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'$_3$ wherein:
  - X_2 is a single bond or,

    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:

    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,

    2) OR_5, $=NR_5$ or,

    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

    cycloalkyl,

    cycloalkenyl,

    aryl,

    heterocycle,

    or a polycyclic group;

    each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

    - X_3 is:

      a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene, a divalent heterocycle or a divalent polycyclic group, and,

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- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5;

wherein,

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-$N(R_{19})$-R_{18} in which X_5 is a single bond or lower alkyl and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;
  - X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or

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several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;
- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier, with the proviso that the compound of formula (I) is not 4-[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-butyric acid ethyl ester, or, 4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-butyric acid ethyl ester.

17. A pharmaceutical composition according to claim 16, comprising a compound of formula (I), in which R1, R2, R3 and Y are as defined in claim 18, with the proviso that when R1 is C(=O)-H, then R2 does not represent $(CH2)_3$-C(=O)OCH_2CH_3.

18. Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 15, together with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to claim 16, 17 or 18, for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant.

20. Method for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant, comprising administering to a mammal, particularly a human, in need thereof, an effective amount of compound of formula (I) according any of claims 1 to 15.

21. Method according to claim 20, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

22. Method according to claim 20, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

23. Use of a compound of formula (I) according to any one of claims 1 to 15, for the manufacture of a medicament for the treatment of diseases for which treatment by a PDE7 inhibitor is relevant.

24. Use according to claim 23, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

25. Use according to claim 23, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

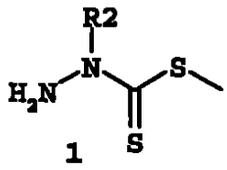
26. A compound of formula (I) as defined in any one of claims 1 to 15, as a medicament.

27. A process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15 in which Y is S, comprising the following steps:

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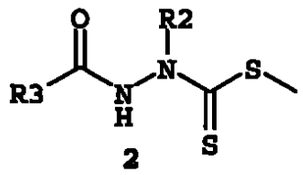
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(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with carbon disulphide and MeX where X is a leaving group to obtain a compound of formula 1



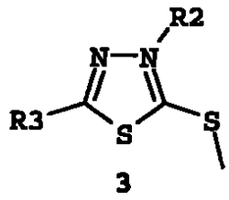
1

(b) reaction of the S-methyldithiocarbazate 1 with an acyl chloride R3COCl in which R3 is as defined in claim 1 to to obtain an acylated methyldithiocarbazate 2



2

(c) cyclization of the acylated methyldithiocarbazate 2 into a 1,3,4-thiadiazole 3



3

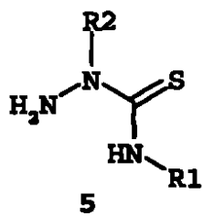
(d) reaction of the 1,3,4-thiadiazole 3 with an amine $R1NH_2$ in which R1 is as defined in claim 1, to obtain the compound of formula (I) in which Y is S,

(e) isolating the compound of formula (I).

28. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

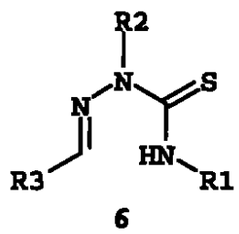
(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1 in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5

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(b) reaction of the thiosemicarbazide 5 with an aldehyde R3CHO in which R3 is as defined in claim 1, to obtain the thiosemicarbazone 6



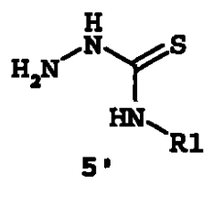
6

(c) cyclization of the thiosemicarbazone 6 into the compound of formula (I) in which Y is S,

(d) isolating the compound of formula (I).

29. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

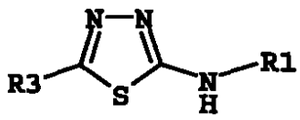
(a) reaction of a carboxylic acid R3COOH in which R3 is as defined in claim 1, with the following thiosemicarbazide 5'



5'

to obtain the 1,3,4-thiadiazole 7

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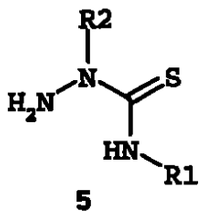
7

(b) reaction of the 1,3,4-thiadiazole 7 with R2X, in which R2 is as defined in claim 1 and X is a leaving group to obtain the compound of formula (I) in which Y is S

(c) isolating the compound of formula (I).

30. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH, in which R3 is as defined in claim 1, with the following thiosemicarbazide 5



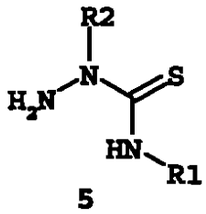
5

to obtain the final compound of formula I in which Y is S,

(b) isolating the compound of formula (I).

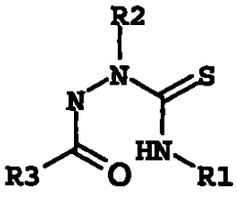
31. Process for the preparation of a 1,3,4-oxadiazole of formula (I) according to any one of claims 1 to 11 or 13, in which Y is O, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$, in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1, in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5,



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(b) reaction of the thiosemicarbazide 5 with R3-C(=O)Cl, in which R3 is as defined in claim 1, to form the desired thiosemicarbazide 8



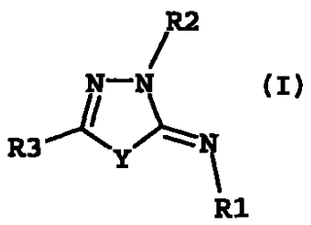
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(c) cyclization of the thiosemicarbazide 8 into the final compound of formula I in which Y is O,

(d) isolating the compound of formula (I).

CLAIMS

1. A compound having the following formula (I),



in which

- Y is O or S;
- R1 is:

C_4-C_{10} alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are

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selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_4-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
2) $COOR_5$, OR_5, SO_2R_5,
3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
    2) OR_5, $=NR_5$ or,
    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=N\text{-}SO_2NH_2)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$
  4) heterocycle optionally substituted with one or several groups R_5;

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl

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optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-$N(R_{19})$-R_{18} in which X_5 is a single bond or lower alkylene and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;

- X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21},or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-$N(R_{19})$-R_{18} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;

- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

with the proviso that,

- when R1 is phenyl, it bears at least one substituent other than H,

- when X_2 is a single bond and both R1 and R'_3 are phenyl, each of R1 and R'_3 bear at least one substituent other than H,

- when X_2 is a single bond and R'_3 is phenyl, R'_3 is not substituted by an ester or a carboxylic acid in the ortho position,

- When Y represents O and R3 represents a phenyl or a cycloalkyl, unsubstituted or substituted, then R1 is other than substituted 1,3,5-triazine,

- the atom of R3 which is linked to the thiadiazole group is a carbon atom,

with the exclusion of the following compounds,

(3,5-diphenyl-3H-[1,3,4]oxadiazol-2-ylidene)-naphthalen-2-yl-amine,
tert-butyl-(3-*tert*-butyl-5-phenyl-3*H*-[1,3,4]oxadiazol-2-ylidene)-amine,
2-[(3-methyl-5-phenyl-3H-[1,3,4]oxadiazol-2-ylideneamino)-methylene]-malonic acid diethyl ester,
[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]phenyl-methanone,
(4-methoxy-phenyl)-[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-methanone,
[4-(4-fluoro-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl-methanone,
1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-methanone,
1-[4-Phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,
1-Phenyl-1-(4-phenyl-5-*p*-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,
Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethyl-cyclopent-1-enylmethyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
2-(3,5-Diphenyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,
2-[3-Phenyl-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,
2-[5-(1-Phenyl-methanoyl)-3-*p*-tolyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,
2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

2. A compound according to claim 1 in which R1, R2, R3 and Y are as defined in claim 1 with the proviso that, when R2 is a phenyl, unsubstituted or substituted whith 1 to 3 chorine or with a methyl, then R3 does not represent C(=O)-phenyl, C(=O)-thienyl, phenyl or CH_2-(2,3,3-trimethyl-cyclopent-1-enyl).

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3. A compound of formula (I) as defined in claim 1 or 2, in which R1 is:

C_4-C_6 alkyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:
  1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
  3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$,
  wherein R_5 is selected from hydrogen or lower alkyl, optionally substituted with OH, and R_6, R_9 and R_{10} are identical or different and are selected from hydrogen or lower alkyl.

4. A compound as defined in any one of claims 1 to 3 in which R2 is lower alkyl.

5. A compound as defined in any one of claims 1 to 4 in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, and,
- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,

or a polycyclic group;
each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

6. A compound as defined in any one of claims 1 to 5, in which R1 is:
cycloalkyl, preferably cyclohexane,
cycloalkenyl,
aryl, preferably phenyl,
or a bicyclic group;
each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$.
  wherein R_5 and R_6 are identical or different and are selected from hydrogen or methyl.

7. A compound as defined in any one of claims 1 to 6, in which R2 is CH_3.

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8. A compound as defined in any one of claims 1 to 7 in which R3 is X_2-R'$_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or -CH_2-, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

9. A compound according to claims 3, 4 and 5.

10. A compound according to claims 6, 7 and 8.

11. A compound as defined in claim 1 in which R1 is:

cyclohexane,
phenyl
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:

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1) H, halogen, CF_3,
2) COOH, OH,
3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same or different and are selected from H or lower alkyl,

R2 is CH_3, and,

R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond, and,
- R_{17} is:
  1) CN, OH, CF_3, =O, C_1-C_6 alkoxy, halogen,
  2) $COOR_5$, SO_2R_5,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 or R_6,
  4) heterocycle optionally substituted with one or several groups R_5.

12. A compound as defined in any one of claims 1 to 11 in which Y is S.

13. A compound as defined in any one of claims 1 to 11 in which Y is O.

14. A compound selected from the group consisting of:
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4] thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,

(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol,
2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol,
{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-propyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol,
tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-isopropyl-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,

N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine,
(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine,
3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine,
(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide,
Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol,
3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid,

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3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid,
(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine,
(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[5-(3-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

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5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol,
compound with trifluoro-methanesulfonic acid
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,

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2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide,
[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol,
6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol,
Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol,
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-*N*-(2H-tetrazol-5-yl)-benzamide hydrochloride salt,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
2-({1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-methanoyl}-amino)-3-(4-hydroxy-phenyl)-propionic acid, compound with 2,2,2-trifluoro-acetic acid,

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(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,
N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,

[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,

Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,

(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine,

Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

5-[5-(4-Cyano-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,

4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

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4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester,
4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

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4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
(1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,

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3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,

[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine,

[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine,

3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,

N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide,

3-[5-(4-Chloro-phenyl)-3-methyl-3H/-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile,

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine,

3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-methyl-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide,

[5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine,
[5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

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N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide,
[5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
(E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine,
[5-(*N*-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(*N*-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-urea,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester, and,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide.

15. A compound according to claim 14, selected from the group consisting of:

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,

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5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-

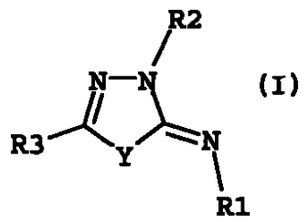
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[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-
yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-
benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-
benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-
benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-
phenyl)-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-
phenyl)-propionic acid; compound with 2,2,2-trifluoro-
acetic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-
benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-
propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,

N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide, and,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea.

16. Pharmaceutical composition comprising a compound of formula (I),



wherein:

- Y is O or S;
- R1 is:

C_1-C_{10} alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a polycyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or a divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:

lower alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,

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aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'$_3$ wherein:
  - X_2 is a single bond or,

a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,

2) OR_5, $=NR_5$ or,

3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

cycloalkyl,

cycloalkenyl,

aryl,

heterocycle,

or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

  - X_3 is:

a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene, a divalent heterocycle or a divalent polycyclic group, and,

- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=N\text{-}SO_2NH_2)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5;

wherein,

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, $X_5\text{-}N(R_{18})(R_{19})$ in which X_5 is a single bond or lower alkyl and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;
  - X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or

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several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{18})(R_{19}) in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;

- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier, with the proviso that the compound of formula (I) is not 4-[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-butyric acid ethyl ester, or, 4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-butyric acid ethyl ester.

17. A pharmaceutical composition according to claim 16, comprising a compound of formula (I), in which R1, R2, R3 and Y are as defined in claim 18, with the proviso that when R1 is C(=O)-H, then R2 does not represent $(CH2)_3$-C(=O)OCH_2CH_3.

18. Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 15, together with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to claim 16, 17 or 18, for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant.

20. Method for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant, comprising administering to a mammal, particularly a human, in need thereof, an effective amount of compound of formula (I) according any of claims 1 to 15.

(15)

21. Method according to claim 20, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

22. Method according to claim 20, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

23. Use of a compound of formula (I) according to any one of claims 1 to 15, for the manufacture of a medicament for the treatment of diseases for which treatment by a PDE7 inhibitor is relevant.

24. Use according to claim 23, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

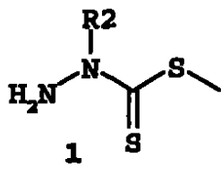
25. Use according to claim 23, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

26. A compound of formula (I) as defined in any one of claims 1 to 15, as a medicament.

27. A process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15 in which Y is S, comprising the following steps:

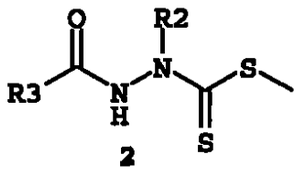
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(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with carbon disulphide and MeX where X is a leaving group to obtain a compound of formula 1



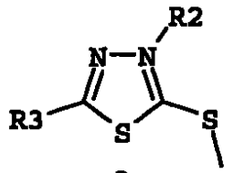
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(b) reaction of the S-methyldithiocarbazate 1 with an acyl chloride R3COCl in which R3 is as defined in claim 1 to to obtain an acylated methyldithiocarbazate 2



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(c) cyclization of the acylated methyldithiocarbazate 2 into a 1,3,4-thiadiazole 3



3

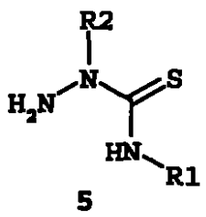
(d) reaction of the 1,3,4-thiadiazole 3 with an amine $R1NH_2$ in which R1 is as defined in claim 1, to obtain the compound of formula (I) in which Y is S,

(e) isolating the compound of formula (I).

28. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

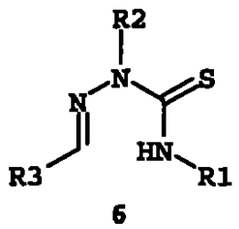
(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1 in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5

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(b) reaction of the thiosemicarbazide 5 with an aldehyde R3CHO in which R3 is as defined in claim 1, to obtain the thiosemicarbazone 6



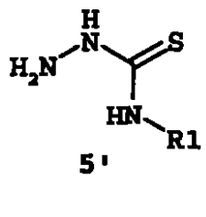
6

(c) cyclization of the thiosemicarbazone 6 into the compound of formula (I) in which Y is S,

(d) isolating the compound of formula (I).

29. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

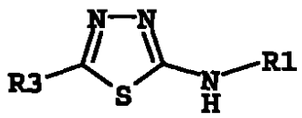
(a) reaction of a carboxylic acid R3COOH in which R3 is as defined in claim 1, with the following thiosemicarbazide 5'



5'

to obtain the 1,3,4-thiadiazole 7

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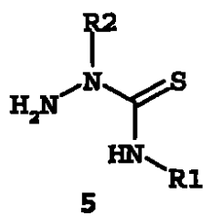
7

(b) reaction of the 1,3,4-thiadiazole 7 with R2X, in which R2 is as defined in claim 1 and X is a leaving group to obtain the compound of formula (I) in which Y is S

(c) isolating the compound of formula (I).

30. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH, in which R3 is as defined in claim 1, with the following thiosemicarbazide 5



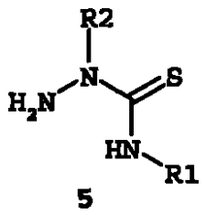
5

to obtain the final compound of formula I in which Y is S,

(b) isolating the compound of formula (I).

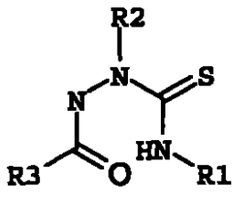
31. Process for the preparation of a 1,3,4-oxadiazole of formula (I) according to any one of claims 1 to 11 or 13, in which Y is O, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$, in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1, in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5,



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(b) reaction of the thiosemicarbazide 5 with R3-C(=O)Cl, in which R3 is as defined in claim 1, to form the desired thiosemicarbazide 8



8

(c) cyclization of the thiosemicarbazide 8 into the final compound of formula I in which Y is O,

(d) isolating the compound of formula (I).

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[en el margen superior izquierdo aparece el logo de Pfizer]

División Legales, Departamento de Patentes

Pfizer

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PAÍSES BAJOS

5 de diciembre de 2002

Fax: +31 70 340 3016

& confirmación via e-mail

Nuestra Ref: 018155 (A-305)

DH/MB

Re: Solicitud internacional No. PCT/EP01/11330

Solicitante: Warner-Lambert Company

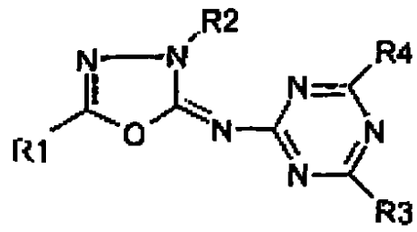
De mi mayor consideración,

Por la presente damos respuesta a la segunda opinión escrita relacionada con la solicitud de referencia. Sírvase encontrar adjunto dos pliegos de reivindicaciones enmendadas, de los cuales uno contiene enmiendas subrayadas. Las enmiendas se detallan a continuación.

El examinador consideró que las reivindicaciones 1-5, 7-9, 13 y 31 carecen de novedad en vista de D1.

D1: DD251979 (1987

D1 revela compuestos de fórmula



en donde R1 y R2 se seleccionan de alquilo o arilo y R3 y R4 se seleccionan de alcoxi, ariloxi, alquiltio, ariltio, alquilamino, arilamino, dialquilamino, diarilamino, alquilarilamino, opcionalmente hidrazina sustituida o OH, Cl.

Con el fin de superar las objeciones del examinador, se ha incorporado el siguiente descargo en la reivindicación 1:

"cuando R3 representa un fenilo o un cicloalquilo, susituido o no sustituido, e Y representa O, entonces R1 es diferente a 1,3,5-triazina sustituida"

[aparece una frase en un tercer idioma]

23-25, avenue du Docteur Lannelongue-75668 Paris Cedex 14-Tel.: 01 58 07 30 00- Fax: 01 58 07 30 01

[aparece una oración en un tercer idioma]

Las enmiendas precedentes deben superar las objeciones del examinador.

Atentamente,

[firma ilegible]

Denise Hirsch

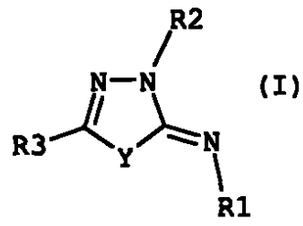
Abogada de patentes europea.

Ajunto: 2 pliegos de reivindicaciones

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REIVINDICACIONES

1. Un compuesto que tiene la siguiente fórmula (I),



en donde

- Y es O o S;

- R_1 es:

  alquilo de C_4-C_{10},

  alquenilo de C_2-C_{10},

  alquinilo de C_2-C_{10},

  cicloalquilo,

  cicloalquenilo,

  heterociclo,

  arilo,

  o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

  un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y,

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- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_4-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

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3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es $X_2-R'_3$ en donde:
  - X_2 es un solo enlace o,

    un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

    1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

    2) OR_5, $=NR_5$ o,

    3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y

    se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'3 es:

  cicloalquilo,

  cicloalquenilo,

  arilo,

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heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo policíclico divalente, y,

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

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- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;
- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenileno de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-N(R_{18})(R_{19}) en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;
- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policíclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos se sustituyen optativamente con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;
- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o X_5-N(R_{18})(R_{19}) en donde X_5 es un

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solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

con la condición de que,

- cuando R_1 es fenilo, lleva por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y tanto R_1 como R'_3 son fenilo, cada uno de R_1 y R'_3 llevan por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y R'_3 es fenilo, R'_3 no se sustituye con un éster o un ácido carboxílico en la posición orto,

- cuando Y representa O y R_3 representa un fenilo o un cicloalquilo, no sustitudo o sustituido, entonces R_1 es diferente de 1,3,5-triazina sustituida,

- el átomo de R_3 que está unido al grupo tiadiazol es un átomo de carbono,

excluyendo los siguientes compuestos,

(3,5-difenil-3H-[1,3,4]oxadiazol-2-iliden)-naftalen-2-il-amina,

terc-butil-(3-terc-butil-5-fenil-3H-[1,3,4]oxadiazol-2-iliden)-amina,

dietil éster del ácido 2-[(3-metil-5-fenil-3H-[1,3,4]oxadiazol-2-ilidenamino)-metilen]-malónico,

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[4-(4-metoxi-fenil)-5-(4-metoxi-fenilamino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]fenil-metanona,

(4-metoxi-fenil)-[4-(4-metoxi-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-metanona,

[4-(4-fluoro-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-fenil-metanona,

1-Fenil-1-[4-fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-metanona,

1-[4-Fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-1-tiofen-2-il-metanona,

1-Fenil-1-(4-fenil-5-*p*-tolilimino-4,5-dihidro-[1,3,4]tiadiazol-2-il)-metanona,

Ciclohexil-[3-(2,4,6-tricloro-fenil)-5-(2,3,3-trimetil-ciclopent-1-enilmetil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

2-(3,5-Difenil-3*H*-[1,3,4]tiadiazol-2-ilidenamino)-1,4-difenil-but-2-en-1,4-diona,

Dimetil éster del ácido 2-[3-Fenil-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico,

Dimetil éster del ácido 2-[5-(1-Fenil-metanoil)-3-*p*-tolil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico, y,

Dimetil éster del ácido 2-[3-(4-Cloro-fenil)-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico.

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2. Un compuesto de acuerdo con la reivindicación 1, en donde R_1, R_2, R_3 e Y son lo definido en la reivindicación 1 con la condición de que, cuando R_2 es fenilo, no sustituido o sustituido con 1 a 3 cloro o con un metilo, entonces R_3 no representa C(=O)-fenilo, C(=O)-tienilo, fenilo o CH_2-(2,3,3-trimetil-ciclopent-1-enilo).

3. Un compuesto de la fórmula (I) definido en la reivindicación 1 o 2, en donde porque R_1 es:

alquilo de C_4-C_6,

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo biciclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace, un heterociclo divalente o un alquileno inferior, y
- R_4 se selecciona de:

1) H, =O, halógeno, CN, haloalquilo inferior, preferentemente CF_3, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

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3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=S)NR_9R_{10}$,

en donde R_5 se selecciona de hidrógeno o alquilo inferior, optativamente sustituido con OH, y R_6, R_9 y R_{10} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior.

4. Un compuesto definido en cualquiera de las reivindicaciones 1 a 3, en donde R_2 es alquilo inferior.

5. Un compuesto definido en cualquiera de las reivindicaciones 1 a 4, en donde R_3 es X_2-R'_3 en donde

- X_2 es solo enlace, alquileno de C_1-C_4, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, y
- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico,

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o alquileno inferior, y

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- R_{17} es:

  1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

  4) heterociclo optativamente sustituido con uno o varios grupos R_5.

6. Un compuesto definido en cualquiera de las reivindicaciones 1 a 5, en donde R_1 es:

cicloalquilo, preferentemente ciclohexano,

cicloalquenilo,

arilo, preferentemente fenilo,

o un grupo biciclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferente, en donde:

- X_1 es solo enlace o un heterociclo divalente y,
- R_4 se selecciona de:

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1) H, halógeno, CF_3, =O,

2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$.

en donde R_5 y R_6 son idénticos o diferentes y se seleccionan de hidrógeno o metilo.

7. Un compuesto definido en cualquiera de las reivindicaciones 1 a 6, en donde R_2 es CH_3.

8. Un compuesto definido en cualquiera de las reivindicaciones 1 a 7, en donde R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6, y
- R'_3 es:

cicloalquilo,

arilo, preferentemente fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o $-CH_2-$, y
- R_{17} es:

1) H, CN, CF_3, halógeno, NO_2,

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2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=N-CN)NR_9R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

9. Un compuesto de acuerdo con las reivindicaciones 3, 4, y 5.

10. Un compuesto de acuerdo con las reivindicaciones 6, 7 y 8.

11. Un compuesto definido en la reivindicación 1, en donde R_1 es:
ciclohexano,
fenilo
o un grupo bicíclico;
cada uno optativamente susituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es solo enlace o un heterociclo divalente, y
- R_4 se selecciona de:

1) H, halógeno, CF_3,

2) COOH, OH,

3) $C(=O)NR_7R_8$ en donde R_7 y R_8 son iguales o diferentes y se seleccionan de H o alquilo inferior,

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R_2 es CH_3, y

R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6

y

- R'_3 es:

fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace, y
- R_{17} es:

1) CN, OH, CF_3, =O, alcoxi de C_1-C_6, halógeno,

2) $COOR_5$, SO_2R_5,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 o R_6,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

12. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es S.

13. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es O.

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14. Un compuesto seleccionado del grupo formado por:

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido (1R*, 2R*)-2-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fenil-etanol,

2-{2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-etanol,

{1-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclopentil}-metanol,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2,5,6-trifluoro-benzoico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-propil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclobutil-amina,

3-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-azepan-2-ona,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclopentil-amina,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-cicloheptil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-3-metil-butan-1-ol,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-metil-propan-1-ol,

terc-Butil-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-isopropil-amina,

Ácido 4-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(1-etil-propil)-amina,

4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

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N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,2-diamina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-fluoro-fenil)-amina,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,4-diamina,

(1R*, 2S*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-trifluorometil-fenil)-amina,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

(1-Aza-biciclo[2.2.2]oct-3-il)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

(R)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

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[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-fluoro-fenil)-amina,

(3-Cloro-fenil)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ácido {3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-acético,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzamida,

Biciclo[2.2.1]hept-2-il-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

(1R*, 2R*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

5-(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-2-metoxi-fenol,

Ácido 3-(5-ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-4-hidroxi-benzoico,

(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-(3-metanosulfonil-fenil)-amina,

(1R*,2R*)-2-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ciclohexil-[5-(2,4-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(2-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[3-metil-5-(4-trifluorometil-fenil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-piridin-4-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[5-(3-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

Ciclohexil-[5-(3-metoxi-4-nitro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2,4-Dicloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Ciclohexil-(3-metil-5-tiofen-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[5-(3,5-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-[5-(2-etil-5-metil-2H-pirazol-3-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Cloro-2,6-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-(5-isoxazol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[3-metil-5-(5-piridin-2-il-tiofen-2-il)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-6-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

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2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

(5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

2-Cloro-5-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dietilamino-etil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-propil)-N-etil-bencenosulfonamida,

Metil éster del ácido [5-(4-Cloro-fenil)-2-ciclohexilimino-[1,3,4]tiadiazol-3-il]-acético,

Metil éster del ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-hidroxi-etil)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2-diol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,6-dimetoxi-fenol,

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6-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-piridin-2-ol,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2,3-triol,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinolin-8-ol,

Ciclohexil-(3-metil-5-pirazin-2-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

5-[(E)-2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-vinil]-2-metoxi-fenol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol,

Ciclohexil-(3-metil-5-quinolin-8-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

4-(5-Ciclohexilimino-4-methyl-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

[5-(5-Cloro-1H-indol-2-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina; compuesto con ácido trifluoro-metanesulfónico,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

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5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

Ciclohexil-[5-(3,4-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Bromo-4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[5-(4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-fenil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-hidroxi-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

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Sal de clorhidrato de 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-*N*-(2H-tetrazol-5-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

Ciclohexil-{5-[4-(1-etil-1H-tetrazol-5-il)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isobutil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

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4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-N-metil-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-1-(3-hidroximetil-piperidin-1-il)-metanona,

terc-Butil éster del ácido 2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido 2-((1-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-metanoil)-amino)-3-(4-hidroxi-fenil)-propiónico, compuesto con ácido 2,2,2-trifluoro-acético,

terc-Butil éster del ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido (S)-2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-piridin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-[4-(4-fluoro-fenil)-piperazin-1-il]-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

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[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-pirimidin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-metil-piperazin-1-il)-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(1-etil-pirrolidin-2-ilmetil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-Bencil-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-1)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

[5-(4-((N-ciano-N'-etilmorfolin)-carboximidamido)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

Ciclohexil-(3-metil-5-piridin-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

(5-Benzo[1,3]dioxol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-ciclohexil-amina,

Ciclohexil-[3-metil-5-(3,4,5-trimetoxi-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

Ácido 5-[5-(4-Ciano-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(cis-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[4-Metil-5-(trans-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

(1R*, 3R*))-3-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ácido 4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-morfolin-4-il-etil)-benzamida,

Ácido 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

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4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

N-terc-Butil-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(1,1-dimetil-3-oxo-butil)-4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(2-Ciano-1,2,2-trimetil-etil)-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Metil éster del ácido 1-{4-[5-((1R*,3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoilamino}-ciclopropanocarboxílico,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-benzamida,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Ácido 5-[5-(4-Carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

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4-[4-Metil-5-(4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[4-Metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3,3-Difluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Fluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

(1R*,3R*)-3-{3-Metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-ilidenamino}-ciclohexanol,

Ácido 3-[5-(4-cloro-fenyl)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

Ácido 3-[5-(4-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 2-fluoro-5-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-piperidin-1-il amina,

[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(tetrahidro-piran-4-il)-amina,

Ácido 3-[5-(4-acetilamino-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

N-{4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

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N-{4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{5-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-piridin-2-il}-acetamida,

3-[5-(4-Cloro-fenil)-3-metil-3H/-[1,3,4]tiadiazol-2-ilidenamino]-benzonitrilo,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-N-hidroxi-benzamidina,

3-{3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-metil-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzonitrilo,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzamida,

[5-(4-Bromo-3-metoxi-fenil)-3-metil-2,3-dihidro-[1,3,4]tiadiazol-2-il]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-hidroxi-benzamida,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-nitro-benzoico,

Metil éster del ácido 2-amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Metil éster del ácido 2-acetilamino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-1H-quinazolin-2,4-diona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

Metil éster del ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

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Ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[3-metil-5-piridin-2-il-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-Cloro-3-sulfamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-{3-metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-iliden}-amina,

Ciclohexil-[3-metil-5-(4-nitro-fenil)-3H-[1,3,4] tiadiazol-2-iliden]-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenilamina,

[5-(4-(N-ciano-N'-(2-dimetilaminoetil)-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida,

[5-(4-(bis-etilsulfonilamino)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(1-(2-dimetilaminoetil)amino-2-nitro-vinilamino)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

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(E)-*N*^{1}-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-2-nitro-eten-1,1-diamina,

[5-(*N*-ciano-*N'*-metil-4-carboximidamido-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(N-ciano-N'-amino-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-amida del ácido etanosulfónico,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-fenil]-urea,

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Metil éster del ácido 2-cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Metil éster del ácido 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzoico y

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzamida

15. Un compuesto de acuerdo con la reivindicación 14, seleccionado del grupo formado por:

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

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2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

terc-butil éster del ácido 2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

metil éster del ácido 2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

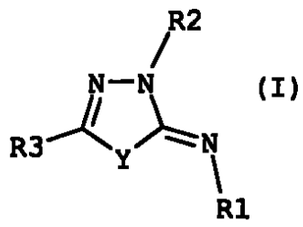
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7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida, y

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea.

16. Una composición farmacéutica que comprende un compuesto de la fórmula (I)



(I)

en donde:

- Y es O o S;

- R_1 es:

alquilo de C_1-C_{10},

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

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arilo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es $X_2-R'_3$ en donde:
- X_2 es un solo enlace o,

un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

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- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo heterocíclico divalente, y

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, bioisóstero de ácido carboxílico, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

en donde,

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenilo de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-N(R_{18})(R_{19})

en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policiclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos optativamente se sustituyen con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo

N(R_{19})

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inferior, arilo, heterociclo, SO_2NH_2 o X_5-N-R_{18} en donde X_5 es un solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

junto con un portador farmacéuticamente aceptable,

con la condición de que el compuesto de la fórmula (I) no sea etil éster del ácido 4-[2-Formilimino-5-(4-metoxi-fenil)-[1,3,4] tiadiazol-3-il]-butírico, o

etil éster del ácido 4-[5-(4-cloro-fenil)-2-formilimino-[1,3,4]tiadiazol-3-il]-butírico.

17. Una composición farmacéutica de acuerdo con la reivindicación 16, que comprende un compuesto de la fórmula (I), en donde R_1, R_2, R_3 e Y son lo definico en la reivindicación 18, con la condición de que cuando R_1 es C(=O)-H, R_2 no represente $(CH_2)_3$-$C(=O)OCH_2CH_3$.

18. Una composición farmacéutica que comprende un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, junto con un portador farmacéuticamente aceptable.

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19. Una composición farmacéutica de acuerdo con la reivindicación 16, 17 o 18, para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante.

20. Un método para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante, que comprende administrar a un mamífero, particularmente a un humano, que lo necesita, una cantidad eficaz de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15.

21. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se debe tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

22. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis

múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

24. El uso de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, para la fabricación de un medicamento para el tratamiento de enfermedades para las cuales el tratamiento con un inhibidor de PDE7 es relevante.

24. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

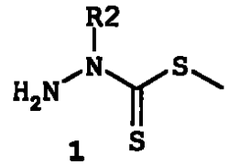
25. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

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26. Un compuesto de la fórmula (I), definido en cualquiera de las reivindicaciones 1 a 15, como medicamento.

27. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

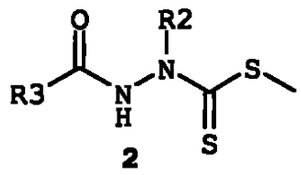
(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reividindicación 1, con disulfuro de carbono y MeX donde X es un grupo saliente para obtener un compuesto de la fórmula 1



1

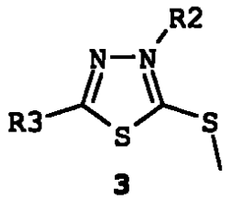
(b) reacción del S-metilditiocarbazato 1 con un cloruro de acilo R_3COCl en donde R_3 es lo definido en la reivindicación 1 para obtener un metilditiocarbazato acilado 2

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2

(c) ciclación del metilditiocarbazato acilado 2 en un 1,3,4-tiadiazol 3



3

(d) reacción del 1,3,4-tiadiazol 3 con una amina R_1NH_2 en donde R_1 es lo definido en reivindicación 1, para obtener el compuesto de la fórmula (I) en donde Y es S,

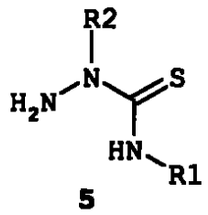
(e) aislación del compuesto de la fórmula (I).

28. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$ en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5

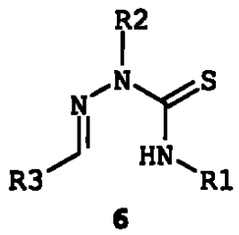
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(b) reacción de la tiosemicarbazida 5 con un aldehído R_3CHO en donde R_3 es lo definido en la reivindicación 1, para obtener la tiosemicarbazona 6



6

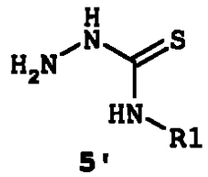
(c) ciclación de la tiosemicarbazona 6 en el compuesto de la fórmula (I) en donde Y es S,

(d) aislación del compuesto de la fórmula (I).

29. El proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

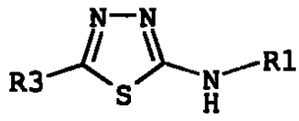
(a) reacción de un ácido carboxílico R_3COOH en donde R_3 es lo definido en reivindicación 1, con la siguiente tiosemicarbazida 5'

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5'

para obtener el 1,3,4-tiadiazol 7

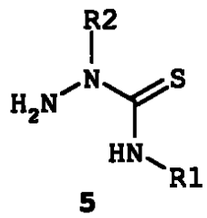


(b) reacción del 1,3,4-tiadiazol 7 con R_2X, en donde R_2 es lo definido en la reivindicación 1 y X es un grupo saliente para obtener el compuesto de la fórmula (I) en donde Y es S

(c) aislación del compuesto de la fórmula (I).

30. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 14, que comprende los siguientes pasos:

(a) reacción de un ácido carboxílico R_3COOH, en donde R_3 es lo definido en la reivindicación 1, con la siguiente tiosemicarbazida 5



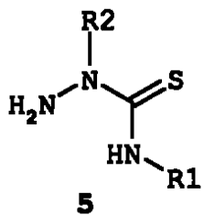
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para obtener el compuesto final de la fórmula I en donde Y es S,

(b) aislación del compuesto de la fórmula (I).

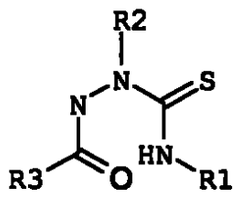
31. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 11 o 13, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de una hidrazina sustituida R_2NHNH_2, en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$, en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5,



5

(b) reacción de la tiosemicarbazida 5 con R_3-C(=O)Cl, en donde R_3 es lo definido en la reivindicación 1, para formar la tiosemicarbazida 8 deseada



8

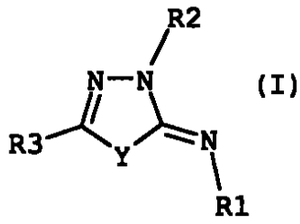
(c) ciclación de la tiosemicarbazida 8 en el compuesto final de la fórmula I en donde Y es O,

(d) aislación del compuesto de la fórmula (I).

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REIVINDICACIONES

1. Un compuesto que tiene la siguiente fórmula (I),



en donde

- Y es O o S;

- R_1 es:

  alquilo de C_4-C_{10},

  alquenilo de C_2-C_{10},

  alquinilo de C_2-C_{10},

  cicloalquilo,

  cicloalquenilo,

  heterociclo,

  arilo,

  o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y,

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- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_4-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

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3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es X_2-R'_3 en donde:
  - X_2 es un solo enlace o,

    un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

    1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

    2) OR_5, $=NR_5$ o,

    3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y

    se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'3 es:

  cicloalquilo;

  cicloalquenilo,

  arilo,

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heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo policíclico divalente, y,

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

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- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenileno de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-N(R_{19})-R_{18} en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policíclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos se sustituyen optativamente con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o X_5-N(R_{19})-R_{18} en donde X_5 es un

solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

con la condición de que,

- cuando R_1 es fenilo, lleva por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y tanto R_1 como R'_3 son fenilo, cada uno de R_1 y R'_3 llevan por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y R'_3 es fenilo, R'_3 no se sustituye con un éster o un ácido carboxílico en la posición orto,

- cuando Y representa O y R_3 representa un fenilo o un cicloalquilo, no sustitudo o sustituido, entonces R_1 es diferente de 1,3,5-triazina sustituida,

- el átomo de R_3 que está unido al grupo tiadiazol es un átomo de carbono,

excluyendo los siguientes compuestos,

(3,5-difenil-3H-[1,3,4]oxadiazol-2-iliden)-naftalen-2-il-amina,

terc-butil-(3-terc-butil-5-fenil-3H-[1,3,4]oxadiazol-2-iliden)-amina,

dietil éster del ácido 2-[(3-metil-5-fenil-3H-[1,3,4]oxadiazol-2-ilidenamino)-metilen]-malónico,

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[4-(4-metoxi-fenil)-5-(4-metoxi-fenilamino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]fenil-metanona,

(4-metoxi-fenil)-[4-(4-metoxi-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-metanona,

[4-(4-fluoro-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-fenil-metanona,

1-Fenil-1-[4-fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-metanona,

1-[4-Fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-1-tiofen-2-il-metanona,

1-Fenil-1-(4-fenil-5-*p*-tolilimino-4,5-dihidro-[1,3,4]tiadiazol-2-il)-metanona,

Ciclohexil-[3-(2,4,6-tricloro-fenil)-5-(2,3,3-trimetil-ciclopent-1-enilmetil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

2-(3,5-Difenil-3*H*-[1,3,4]tiadiazol-2-ilidenamino)-1,4-difenil-but-2-en-1,4-diona,

Dimetil éster del ácido 2-[3-Fenil-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico,

Dimetil éster del ácido 2-[5-(1-Fenil-metanoil)-3-*p*-tolil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico, y,

Dimetil éster del ácido 2-[3-(4-Cloro-fenil)-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico.

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2. Un compuesto de acuerdo con la reivindicación 1, en donde R_1, R_2, R_3 e Y son lo definido en la reivindicación 1 con la condición de que, cuando R_2 es fenilo, no sustituido o sustituido con 1 a 3 cloro o con un metilo, entonces R_3 no representa C(=O)-fenilo, C(=O)-tienilo, fenilo o CH_2-(2,3,3-trimetil-ciclopent-1-enilo).

3. Un compuesto de la fórmula (I) definido en la reivindicación 1 o 2, en donde porque R_1 es:

alquilo de C_4-C_6,

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo biciclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace, un heterociclo divalente o un alquileno inferior, y
- R_4 se selecciona de:

1) H, =O, halógeno, CN, haloalquilo inferior, preferentemente CF_3, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=S)NR_9R_{10}$,

en donde R_5 se selecciona de hidrógeno o alquilo inferior, optativamente sustituido con OH, y R_6, R_9 y R_{10} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior.

4. Un compuesto definido en cualquiera de las reivindicaciones 1 a 3, en donde R_2 es alquilo inferior.

5. Un compuesto definido en cualquiera de las reivindicaciones 1 a 4, en donde R_3 es X_2-R'_3 en donde

- X_2 es solo enlace, alquileno de C_1-C_4, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, y
- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico,

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o alquileno inferior, y

- R_{17} es:

  1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

  4) heterociclo optativamente sustituido con uno o varios grupos R_5.

6. Un compuesto definido en cualquiera de las reivindicaciones 1 a 5, en donde R_1 es:

cicloalquilo, preferentemente ciclohexano,

cicloalquenilo,

arilo, preferentemente fenilo,

o un grupo biciclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferente, en donde:

- X_1 es solo enlace o un heterociclo divalente y,
- R_4 se selecciona de:

1) H, halógeno, CF_3, =O,

2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$.

en donde R_5 y R_6 son idénticos o diferentes y se seleccionan de hidrógeno o metilo.

7. Un compuesto definido en cualquiera de las reivindicaciones 1 a 6, en donde R_2 es CH_3.

8. Un compuesto definido en cualquiera de las reivindicaciones 1 a 7, en donde R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6, y
- R'_3 es:

cicloalquilo,

arilo, preferentemente fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o $-CH_2-$, y
- R_{17} es:

1) H, CN, CF_3, halógeno, NO_2,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=N-CN)NR_9R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

9. Un compuesto de acuerdo con las reivindicaciones 3, 4, y 5.

10. Un compuesto de acuerdo con las reivindicaciones 6, 7 y 8.

11. Un compuesto definido en la reivindicación 1, en donde R_1 es:
ciclohexano,
fenilo
o un grupo bicíclico;
cada uno optativamente susituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es solo enlace o un heterociclo divalente, y
- R_4 se selecciona de:

1) H, halógeno, CF_3,

2) COOH, OH,

3) $C(=O)NR_7R_8$ en donde R_7 y R_8 son iguales o diferentes y se seleccionan de H o alquilo inferior,

R_2 es CH_3, y

R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6 y

- R'_3 es:

fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace, y

- R_{17} es:

1) CN, OH, CF_3, =O, alcoxi de C_1-C_6, halógeno,

2) $COOR_5$, SO_2R_5,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 o R_6,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

12. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es S.

13. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es O.

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14. Un compuesto seleccionado del grupo formado por:

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido (1R*, 2R*)-2-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fenil-etanol,

2-{2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-etanol,

{1-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclopentil}-metanol,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2,5,6-trifluoro-benzoico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-propil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

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[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclobutil-amina,

3-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-azepan-2-ona,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclopentil-amina,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-cicloheptil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-3-metil-butan-1-ol,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-metil-propan-1-ol,

terc-Butil-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-isopropil-amina,

Ácido 4-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(1-etil-propil)-amina,

4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,2-diamina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-fluoro-fenil)-amina,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,4-diamina,

(1R*, 2S*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-trifluorometil-fenil)-amina,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilideñamino]-fenol,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

(1-Aza-biciclo[2.2.2]oct-3-il)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

(R)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

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[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-fluoro-fenil)-amina,

(3-Cloro-fenil)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ácido {3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-acético,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzamida,

Biciclo[2.2.1]hept-2-il-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

(1R*, 2R*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

5-(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-2-metoxi-fenol,

Ácido 3-(5-ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-4-hidroxi-benzoico,

(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-(3-metanosulfonil-fenil)-amina,

(1R*,2R*)-2-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ciclohexil-[5-(2,4-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(2-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[3-metil-5-(4-trifluorometil-fenil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-piridin-4-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[5-(3-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

Ciclohexil-[5-(3-metoxi-4-nitro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2,4-Dicloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Ciclohexil-(3-metil-5-tiofen-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[5-(3,5-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-[5-(2-etil-5-metil-2H-pirazol-3-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Cloro-2,6-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-(5-isoxazol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[3-metil-5-(5-piridin-2-il-tiofen-2-il)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-6-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

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2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

2-Cloro-5-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dietilamino-etil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-propil)-N-etil-bencenosulfonamida,

Metil éster del ácido [5-(4-Cloro-fenil)-2-ciclohexilimino-[1,3,4]tiadiazol-3-il]-acético,

Metil éster del ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-hidroxi-etil)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2-diol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,6-dimetoxi-fenol,

6-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-piridin-2-ol,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2,3-triol,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinolin-8-ol,

Ciclohexil-(3-metil-5-pirazin-2-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

5-[(E)-2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-vinil]-2-metoxi-fenol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol,

Ciclohexil-(3-metil-5-quinolin-8-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

4-(5-Ciclohexilimino-4-methyl-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

[5-(5-Cloro-1H-indol-2-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina; compuesto con ácido trifluoro-metanesulfónico,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

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5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

Ciclohexil-[5-(3,4-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Bromo-4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[5-(4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-fenil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-hidroxi-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

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Sal de clorhidrato de 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-*N*-(2H-tetrazol-5-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

Ciclohexil-{5-[4-(1-etil-1H-tetrazol-5-il)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isobutil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

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4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-N-metil-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-1-(3-hidroximetil-piperidin-1-il)-metanona,

terc-Butil éster del ácido 2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido 2-({1-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-metanoil}-amino)-3-(4-hidroxi-fenil)-propiónico, compuesto con ácido 2,2,2-trifluoro-acético,

terc-Butil éster del ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido (S)-2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-piridin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-[4-(4-fluoro-fenil)-piperazin-1-il]-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

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[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-pirimidin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-metil-piperazin-1-il)-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(1-etil-pirrolidin-2-ilmetil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-Bencil-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-l)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

[5-(4-((N-ciano-N'-etilmorfolin)-carboximidamido)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

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Ciclohexil-(3-metil-5-piridin-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

(5-Benzo[1,3]dioxol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-ciclohexil-amina,

Ciclohexil-[3-metil-5-(3,4,5-trimetoxi-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

Ácido 5-[5-(4-Ciano-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(cis-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[4-Metil-5-(trans-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

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4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

(1R*, 3R*))-3-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ácido 4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-morfolin-4-il-etil)-benzamida,

Ácido 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

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4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

N-terc-Butil-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(1,1-dimetil-3-oxo-butil)-4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(2-Ciano-1,2,2-trimetil-etil)-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Metil éster del ácido 1-{4-[5-((1R*,3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoilamino}-ciclopropanocarboxílico,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-benzamida,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Ácido 5-[5-(4-Carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

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4-[4-Metil-5-(4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[4-Metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3,3-Difluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Fluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

(1R*,3R*)-3-{3-Metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-ilidenamino}-ciclohexanol,

Ácido 3-[5-(4-cloro-fenyl)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

Ácido 3-[5-(4-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 2-fluoro-5-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-piperidin-1-il amina,

[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(tetrahidro-piran-4-il)-amina,

Ácido 3-[5-(4-acetilamino-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

N-{4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

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N-{4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{5-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-piridin-2-il}-acetamida,

3-[5-(4-Cloro-fenil)-3-metil-3H/-[1,3,4]tiadiazol-2-ilidenamino]-benzonitrilo,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-N-hidroxi-benzamidina,

3-{3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-metil-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzonitrilo,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzamida,

[5-(4-Bromo-3-metoxi-fenil)-3-metil-2,3-dihidro-[1,3,4]tiadiazol-2-il]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-hidroxi-benzamida,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-nitro-benzoico,

Metil éster del ácido 2-amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Metil éster del ácido 2-acetilamino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-1H-quinazolin-2,4-diona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

Metil éster del ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

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Ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[3-metil-5-piridin-2-il-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-Cloro-3-sulfamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-{3-metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-iliden}-amina,

Ciclohexil-[3-metil-5-(4-nitro-fenil)-3H-[1,3,4] tiadiazol-2-iliden]-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenilamina,

[5-(4-(N-ciano-N'-(2-dimetilaminoetil)-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida,

[5-(4-(bis-etilsulfonilamino)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(1-(2-dimetilaminoetil)amino-2-nitro-vinilamino)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

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(E)-*N*¹-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-2-nitro-eten-1,1-diamina,

[5-(*N*-ciano-*N'*-metil-4-carboximidamido-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(N-ciano-N'-amino-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-amida del ácido etanosulfónico,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-fenil]-urea,

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Metil éster del ácido 2-cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Metil éster del ácido 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzoico y

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzamida

15. Un compuesto de acuerdo con la reivindicación 14, seleccionado del grupo formado por:
5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,
5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,
2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,
2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,
{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,
2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,
2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

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2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

terc-butil éster del ácido 2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

metil éster del ácido 2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

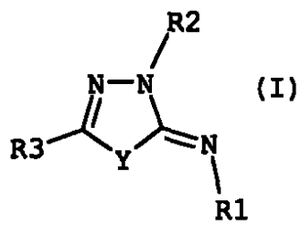
7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida, y

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea.

16. Una composición farmacéutica que comprende un compuesto de la fórmula (I)



en donde:

- Y es O o S;
- R_1 es:

alquilo de C_1-C_{10},

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

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arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es $X_2-R'_3$ en donde:
- X_2 es un solo enlace o,

un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo heterocíclico divalente, y

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, bioisóstero de ácido carboxílico, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

en donde,

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenilo de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-$N(R_{19})$-R_{18}

en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policiclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos optativamente se sustituyen con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo (R_{19})

inferior, arilo, heterociclo, SO_2NH_2 o X_5-N-R_{18} en donde X_5 es un

solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

junto con un portador farmacéuticamente aceptable,

con la condición de que el compuesto de la fórmula (I) no sea etil éster del ácido 4-[2-Formilimino-5-(4-metoxi-fenil)-[1,3,4] tiadiazol-3-il]-butírico, o

etil éster del ácido 4-[5-(4-cloro-fenil)-2-formilimino-[1,3,4]tiadiazol-3-il]-butírico.

17. Una composición farmacéutica de acuerdo con la reivindicación 16, que comprende un compuesto de la fórmula (I), en donde R_1, R_2, R_3 e Y son lo definico en la reivindicación 18, con la condición de que cuando R_1 es C(=O)-H, R_2 no represente $(CH_2)_3$-$C(=O)OCH_2CH_3$.

18. Una composición farmacéutica que comprende un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, junto con un portador farmacéuticamente aceptable.

19. Una composición farmacéutica de acuerdo con la reivindicación 16, 17 o 18, para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante.

20. Un método para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante, que comprende administrar a un mamífero, particularmente a un humano, que lo necesita, una cantidad eficaz de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15.

21. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se debe tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

22. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis

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múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

24. El uso de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, para la fabricación de un medicamento para el tratamiento de enfermedades para las cuales el tratamiento con un inhibidor de PDE7 es relevante.

24. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

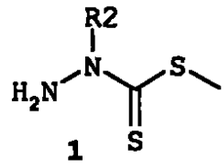
25. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

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26. Un compuesto de la fórmula (I), definido en cualquiera de las reivindicaciones 1 a 15, como medicamento.

27. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

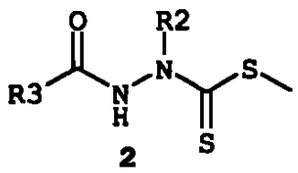
(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reividindicación 1, con disulfuro de carbono y MeX donde X es un grupo saliente para obtener un compuesto de la fórmula 1



1

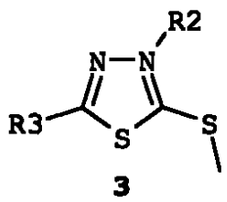
(b) reacción del S-metilditiocarbazato 1 con un cloruro de acilo R_3COCl en donde R_3 es lo definido en la reivindicación 1 para obtener un metilditiocarbazato acilado 2

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2

(c) ciclación del metilditiocarbazato acilado 2 en un 1,3,4-tiadiazol 3



3

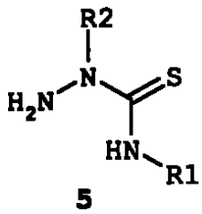
(d) reacción del 1,3,4-tiadiazol 3 con una amina R_1NH_2 en donde R_1 es lo definido en reivindicación 1, para obtener el compuesto de la fórmula (I) en donde Y es S,

(e) aislación del compuesto de la fórmula (I).

28. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

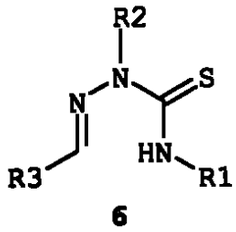
(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$ en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5

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5

(b) reacción de la tiosemicarbazida 5 con un aldehído R_3CHO en donde R_3 es lo definido en la reivindicación 1, para obtener la tiosemicarbazona 6



6

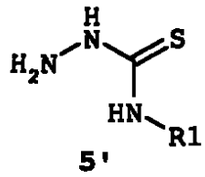
(c) ciclación de la tiosemicarbazona 6 en el compuesto de la fórmula (I) en donde Y es S,

(d) aislación del compuesto de la fórmula (I).

29. El proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

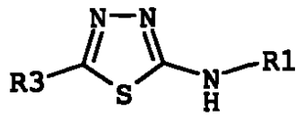
(a) reacción de un ácido carboxílico R_3COOH en donde R_3 es lo definido en reivindicación 1, con la siguiente tiosemicarbazida 5'

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5'

para obtener el 1,3,4-tiadiazol 7



7

(b) reacción del 1,3,4-tiadiazol 7 con R_2X, en donde R_2 es lo definido en la reivindicación 1 y X es un grupo saliente para obtener el compuesto de la fórmula (I) en donde Y es S

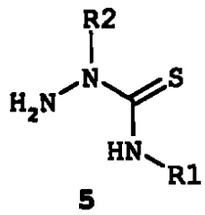
(c) aislación del compuesto de la fórmula (I).

30. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 14, que comprende los siguientes pasos:

(a) reacción de un ácido carboxílico R_3COOH, en donde R_3 es lo definido en la reivindicación 1, con la siguiente tiosemicarbazida

5

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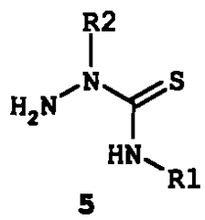
5

para obtener el compuesto final de la fórmula I en donde Y es S,

(b) aislación del compuesto de la fórmula (I).

31. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 11 o 13, en donde Y es S, que comprende los siguientes pasos:

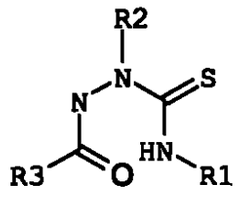
(a) reacción de una hidrazina sustituida R_2NHNH_2, en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$, en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5,



5

(b) reacción de la tiosemicarbazida 5 con R_3-C(=O)Cl, en donde R_3 es lo definido en la reivindicación 1, para formar la tiosemicarbazida 8 deseada

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8

(d) ciclación de la tiosemicarbazida 8 en el compuesto final de la fórmula I en donde Y es O,

(d) aislación del compuesto de la fórmula (I).

PATENT COOPERATION TREATY

10/40 · 1266 · 351.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Hirsch, Denise
WARNER-LAMBERT COMPANY
c/o PARKE-DAVIS
Pfizer Global Research
& Development, Fresnes Laboratories
3-9 rue de la Loge, B.P. 100
F-94265 Fresnes
FRANCE

RECEIVED ON
13. JAN 2003
Patents, Fresnes

PCT 01/35

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	10.01.2003
Applicant's or agent's file reference: 018155-A305 TP	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP01/11330	01/10/2001	02/10/2000

Applicant
WARNER-LAMBERT COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Smith, K Tel.+31 70 340-3479

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
018155-A305		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP01/11330	01/10/2001	02/10/2000
International Patent Classification (IPC) or national classification and IPC C07D285/135		
Applicant WARNER-LAMBERT COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 70 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/04/2002	10.01.2003
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Allard, M Telephone No. +31 70 340 2002

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP01/11330

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-200	as originally filed				

Claims, No.:

1-31	as received on	05/12/2002	with letter of	05/12/2002	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 20-22.

because:

☒ the said international application, or the said claims Nos. 20-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-31
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-19, 23-31

No: Claims -

2. Citations and explanations
see separate sheet

Reference is made to the following document:

D6: WO 99 42089 A (ROCHE DIAGNOSTICS GMBH) 26 August 1999 (1999-08-26)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 20-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Article 33(2) PCT)

Neither the compounds according to claim 1 nor the pharmaceutical compositions according to claim 16 are disclosed in the available prior art; the subject-matter of claims 1-31 is therefore novel.

Inventive step (Article 33(3) PCT)

In the light of the teachings of D6, which is considered to represent the closest prior art and describes imino-thiadiazolopyridines useful as phosphodiesterase inhibitors, the problem underlying and solved by the present application can be seen in the provision of further imino-heterocyclic compounds with the same activity.

The solution to this problem proposed by the present application, *i.e.* the compounds according to claim 1 or the compositions according to claim 16, is not suggested by the available prior art; the subject-matter of claims 1-31 involves therefore an inventive step.

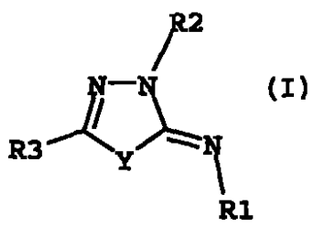
Industrial applicability (Article 33(4) PCT)

The compounds, compositions and methods of claims 1-19 and 23-31 can be used in the pharmaceutical industry.

01282
EPO - DG 1
29. 10. 2002
(43)

CLAIMS

1. A compound having the following formula (I),



(I)

in which

- Y is O or S;
- R1 is:
  - C_4-C_{10} alkyl,
  - C_2-C_{10} alkenyl,
  - C_2-C_{10} alkynyl,
  - cycloalkyl,
  - cycloalkenyl,
  - heterocycle,
  - aryl,
  - or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are

selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_4-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
2) $COOR_5$, OR_5, SO_2R_5,
3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
    2) OR_5, $=NR_5$ or,
    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

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cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=N\text{-}SO_2NH_2)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$
  4) heterocycle optionally substituted with one r several groups R_5;

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl

optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;

- X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;

- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

with the proviso that,

- when R1 is phenyl, it bears at least one substituent other than H,

- when X_2 is a single bond and both R1 and R'_3 are phenyl, each of R1 and R'_3 bear at least one substituent other than H,

- when X_2 is a single bond and R'_3 is phenyl, R'_3 is not substituted by an ester or a carboxylic acid in the ortho position,

- When R3 represents a substituted phenyl and Y is O, then R1 is other than a substituted 1,3,5-triazine,

- the atom of R3 which is linked to the thiadiazole group is a carbon atom,

with the exclusion of the following compounds,

(3,5-diphenyl-3H-[1,3,4]oxadiazol-2-ylidene)-naphthalen-2-yl-

amine,
tert-butyl-(3-tert-butyl-5-phenyl-3*H*-[1,3,4]oxadiazol-2-ylidene)-amine,
2-[(3-methyl-5-phenyl-3H-[1,3,4]oxadiazol-2-ylideneamino)-methylene]-malonic acid diethyl ester,
[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]phenyl-methanone,
(4-methoxy-phenyl)-[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-methanone,
[4-(4-fluoro-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl-methanone,
1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triaz 1-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-methanone,
1-[4-Phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,
1-Phenyl-1-(4-phenyl-5-*p*-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,
Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethyl-cyclopent-1-enylmethyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
2-(3,5-Diphenyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,
2-[3-Phenyl-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,
2-[5-(1-Phenyl-methanoyl)-3-*p*-tolyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,
2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

2. A compound according to claim 1 in which R1, R2, R3 and Y are as defined in claim 1 with the proviso that, when R2 is a phenyl, unsubstituted or substituted whith 1 to 3 chorine or with a methyl, then R3 does not represent C(=O)-phenyl, C(=O)-thienyl, phenyl or CH_2-(2,3,3-trimethyl-cyclopent-1-enyl).

3. A compound of formula (I) as defined in claim 1 r 2, in which R1 is:

C_4-C_6 alkyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:

1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3, lower alkyl, carboxylic acid bioisostere,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$,

wherein R_5 is selected from hydrogen or lower alkyl, optionally substituted with OH, and R_6, R_9 and R_{10} are identical or different and are selected from hydrogen or lower alkyl.

4. A compound as defined in any one of claims 1 to 3 in which R2 is lower alkyl.

5. A compound as defined in any one of claims 1 to 4 in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, and,
- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N\text{-}CN)NR_{15}R_{16}$, $C(=CH\text{-}NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

6. A compound as defined in any one of claims 1 to 5, in which R1 is:
cycloalkyl, preferably cyclohexane,
cycloalkenyl,
aryl, preferably phenyl,
or a bicyclic group;
each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$.
  wherein R_5 and R_6 are identical or different and are selected from hydrogen or methyl.

7. A compound as defined in any one of claims 1 to 6, in which R2 is CH_3.

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8. A compound as defined in any one of claims 1 to 7 in which R3 is X_2-R'$_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or -CH_2-, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N\text{-}CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

9. A compound according to claims 3, 4 and 5.

10. A compound according to claims 6, 7 and 8.

11. A compound as defined in claim 1 in which R1 is:

cyclohexane,
phenyl
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3,

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2) COOH, OH,

3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same or different and are selected from H or lower alkyl,

R2 is CH_3, and,

R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond, and,
- R_{17} is:
  1) CN, OH, CF_3, =O, C_1-C_6 alkoxy, halogen,
  2) $COOR_5$, SO_2R_5,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 or R_6,
  4) heterocycle optionally substituted with one or several groups R_5.

12. A compound as defined in any one of claims 1 to 11 in which Y is S.

13. A compound as defined in any one of claims 1 to 11 in which Y is O.

14. A compound selected from the group consisting of:
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol,

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2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol,
{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-propyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine,
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiaz l-2-ylideneamino]-3-methyl-butan-1-ol,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol,
tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-isopropyl-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine,

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[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine,
(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine,
3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine,
(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide,
Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol,
3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-4-hydroxy-benzoic acid,

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(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine,
(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[5-(3-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

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5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with triflu ro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol,
compound with trifluoro-methanesulfonic acid
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,

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2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide,
[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol,
6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol,
Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol,
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-*N*-(2H-tetrazol-5-yl)-benzamide hydrochloride salt,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
2-({1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-methanoyl}-amino)-3-(4-hydroxy-phenyl)-propionic acid, compound with 2,2,2-trifluoro-acetic acid,

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(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid; compound with 2,2,2-trifluoro-acetic acid,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,
N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,

[5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,

Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,

(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine,

Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

5-[5-(4-Cyano-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,

4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

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4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester,
4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

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4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
(1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,

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3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,

[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine,

[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine,

3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,

N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,

N-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide,

3-[5-(4-Chloro-phenyl)-3-methyl-3H/-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile,

[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine,

3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-methyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide,

[5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-{3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine,
[5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

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N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide,
[5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamin)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
(E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine,
[5-(*N*-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-urea,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester, and,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide.

15. A compound according to claim 14, selected from the group consisting of:

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiaz l-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,

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5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-

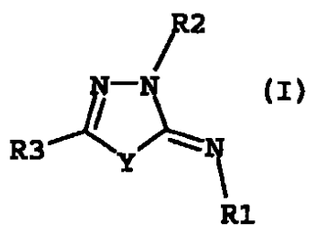
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[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid; compound with 2,2,2-trifluoro-acetic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,

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N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide, and,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea.

16. Pharmaceutical composition comprising a compound of formula (I),



wherein:

- Y is O or S;
- R1 is:

C_1-C_{10} alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a polycyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:

a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or a divalent heterocycle, and,

- R_4 is:

1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:

lower alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,

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aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,

a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,

2) OR_5, $=NR_5$ or,

3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

cycloalkyl,

cycloalkenyl,

aryl,

heterocycle,

or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:

a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene, a divalent heterocycle or a divalent polycyclic group, and,

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- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5;

wherein,

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-$N(R_{19})$-R_{18} in which X_5 is a single bond or lower alkyl and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;
  - X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or

several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{18})-R_{19} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;
- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier, with the proviso that the compound of formula (I) is not 4-[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-butyric acid ethyl ester, or, 4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-butyric acid ethyl ester.

17. A pharmaceutical composition according to claim 16, comprising a compound of formula (I), in which R1, R2, R3 and Y are as defined in claim 18, with the proviso that when R1 is C(=O)-H, then R2 does not represent $(CH2)_3$-C(=O)OCH_2CH_3.

18. Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 15, together with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to claim 16, 17 or 18, for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant.

20. Method for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant, comprising administering to a mammal, particularly a human, in need thereof, an effective amount of compound of formula (I) according any of claims 1 to 15.

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21. Method according to claim 20, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

22. Method according to claim 20, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

23. Use of a compound of formula (I) according to any one of claims 1 to 15, for the manufacture of a medicament for the treatment of diseases for which treatment by a PDE7 inhibitor is relevant.

24. Use according to claim 23, in which the disease t be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

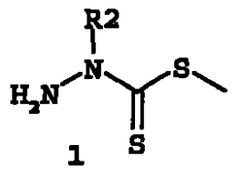
25. Use according to claim 23, in which the disease t be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

26. A compound of formula (I) as defined in any one of claims 1 to 15, as a medicament.

27. A process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15 in which Y is S, comprising the following steps:

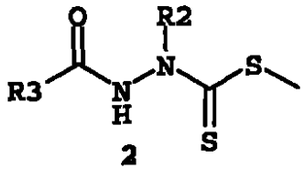
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(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with carbon disulphide and MeX where X is a leaving group to obtain a compound of formula 1



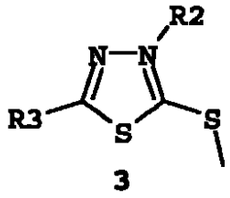
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(b) reaction of the S-methyldithiocarbazate 1 with an acyl chloride R3COCl in which R3 is as defined in claim 1 to to obtain an acylated methyldithiocarbazate 2



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(c) cyclization of the acylated methyldithiocarbazate 2 into a 1,3,4-thiadiazole 3



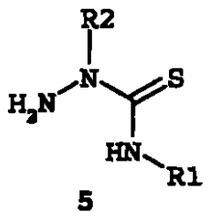
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(d) reaction of the 1,3,4-thiadiazole 3 with an amine $R1NH_2$ in which R1 is as defined in claim 1, to obtain the compound of formula (I) in which Y is S,

(e) isolating the compound of formula (I).

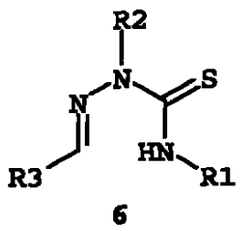
28. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1 in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5



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(b) reaction of the thiosemicarbazide 5 with an aldehyde R3CHO in which R3 is as defined in claim 1, to obtain the thiosemicarbazone 6



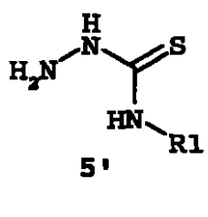
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(c) cyclization of the thiosemicarbazone 6 into the compound of formula (I) in which Y is S,

(d) isolating the compound of formula (I).

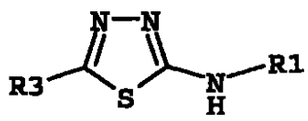
29. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH in which R3 is as defined in claim 1, with the following thiosemicarbazide 5'



5'

to obtain the 1,3,4-thiadiazole 7



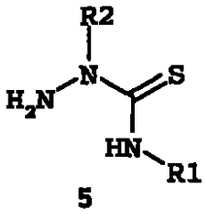
7

(b) reaction of the 1,3,4-thiadiazole 7 with R2X, in which R2 is as defined in claim 1 and X is a leaving group to obtain the compound of formula (I) in which Y is S

(c) isolating the compound of formula (I).

30. Process for the preparation of a 1,3,4-thiadiaz le of formula (I) according to any one of claims 1 to 12, 14 r 15, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH, in which R3 is as defined in claim 1, with the following thiosemicarbazide 5



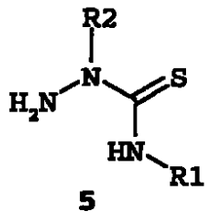
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to obtain the final compound of formula I in which Y is S,

(b) isolating the compound of formula (I).

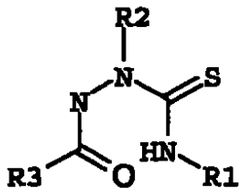
31. Process for the preparation of a 1,3,4-oxadiazole of formula (I) according to any one of claims 1 to 11 or 13, in which Y is O, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$, in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1, in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5,



5

(b) reaction of the thiosemicarbazide 5 with R3-C(=O)Cl, in which R3 is as defined in claim 1, to form the desired thiosemicarbazide 8



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(c) cyclization of the thiosemicarbazide 8 into the final compound of formula I in which Y is O,

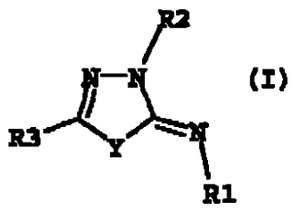
(d) isolating the compound of formula (I).

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CLAIMS

1. A compound having the following formula (I),



(I)

in which

- Y is O or S;
- R1 is:
  - C_4-C_{10} alkyl,
  - C_2-C_{10} alkenyl,
  - C_2-C_{10} alkynyl,
  - cycloalkyl,
  - cycloalkenyl,
  - heterocycle,
  - aryl,
  - or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene or divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are

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selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_4-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,
  aryl;

  each optionally substituted with one or several groups which are the same or different and which are selected from:

  1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
  2) $COOR_5$, OR_5, SO_2R_5,
  3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'_3 wherein:
  - X_2 is a single bond or,
    a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:
    1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,
    2) OR_5, $=NR_5$ or,
    3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

  - R'3 is:

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cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:
  a single bond, lower alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, cycloalkylene, arylene, divalent heterocycle or a divalent polycyclic group, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$
  4) heterocycle optionally substituted with one or several groups R_5;

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl

optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;

- X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-N(R_{19})-R_{18} in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;

- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof,

with the proviso that,

- when R1 is phenyl, it bears at least one substituent other than H,

- when X_2 is a single bond and both R1 and R'_3 are phenyl, each of R1 and R'_3 bear at least one substituent other than H,

- when X_2 is a single bond and R'_3 is phenyl, R'_3 is not substituted by an ester or a carboxylic acid in the ortho position,

- When Y represents O and R3 represents a phenyl or a cycloalkyl, unsubstituted or substituted, then R1 is other than substituted 1,3,5-triazine,

- the atom of R3 which is linked to the thiadiazole group is a carbon atom,

with the exclusion of the following compounds,

(3,5-diphenyl-3H-[1,3,4]oxadiazol-2-ylidene)-naphthalen-2-yl-amine,
tert-butyl-(3-tert-butyl-5-phenyl-3*H*-[1,3,4]oxadiazol-2-ylidene)-amine,
2-[(3-methyl-5-phenyl-3H-[1,3,4]oxadiazol-2-ylideneamino)-methylene]-malonic acid diethyl ester,
[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]phenyl-methanone,
(4-methoxy-phenyl)-[4-(4-methoxy-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-methanone,
[4-(4-fluoro-phenyl)-5-(4-methoxy-phenylimino)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl-methanone,
1-Phenyl-1-[4-phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-methanone,
1-[4-Phenyl-5-(5-trifluoromethyl-2*H*-[1,2,4]triazol-3-ylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-1-thiophen-2-yl-methanone,
1-Phenyl-1-(4-phenyl-5-*p*-tolylimino-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-methanone,
Cyclohexyl-[3-(2,4,6-trichloro-phenyl)-5-(2,3,3-trimethyl-cyclopent-1-enylmethyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
2-(3,5-Diphenyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino)-1,4-diphenyl-but-2-ene-1,4-dione,
2-[3-Phenyl-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester,
2-[5-(1-Phenyl-methanoyl)-3-*p*-tolyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester, and,
2-[3-(4-Chloro-phenyl)-5-(1-phenyl-methanoyl)-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-but-2-enedioic acid dimethyl ester.

2. A compound according to claim 1 in which R1, R2, R3 and Y are as defined in claim 1 with the proviso that, when R2 is a phenyl, unsubstituted or substituted whith 1 to 3 chorine or with a methyl, then R3 does not represent C(=O)-phenyl, C(=O)-thienyl, phenyl or CH_2-(2,3,3-trimethyl-cyclopent-1-enyl).

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3. A compound of formula (I) as defined in claim 1 or 2, in which R1 is:

C_4-C_6 alkyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond, a divalent heterocycle or a lower alkylene, and,
- R_4 is selected from:

1) H, =O, halogen, CN, lower haloalkyl, preferably CF_3, lower alkyl, carboxylic acid bioisostere,
2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$
3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=S)NR_9R_{10}$.
wherein R_5 is selected from hydrogen or lower alkyl, optionally substituted with OH, and R_6, R_9 and R_{10} are identical or different and are selected from hydrogen or lower alkyl.

4. A compound as defined in any one of claims 1 to 3 in which R2 is lower alkyl.

5. A compound as defined in any one of claims 1 to 4 in which R3 is X_2-R'_3 wherein,

- X_2 is a single bond, C_1-C_4 alkylene, C_2-C_6 alkenylene or C_2-C_6 alkynylene, and,
- R'3 is:

cycloalkyl,
cycloalkenyl,
aryl,
heterocycle,

or a polycyclic group;
each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or lower alkylene, and,
- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, cycloalkyl,
  2) $COOR_5$, $C(=O)R_6$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_2R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

6. A compound as defined in any one of claims 1 to 5, in which R1 is:
cycloalkyl, preferably cyclohexane,
cycloalkenyl,
aryl, preferably phenyl,
or a bicyclic group;
each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:
  1) H, halogen, CF_3, =O,
  2) $COOR_5$, OR_5,
  3) $C(=O)NR_5R_6$.
  wherein R_5 and R_6 are identical or different and are selected from hydrogen or methyl.

7. A compound as defined in any one of claims 1 to 6, in which R2 is CH_3.

8. A compound as defined in any one of claims 1 to 7 in which R3 is X_2-R'$_3$ wherein,

- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

cycloalkyl,
aryl, preferably phenyl,
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is a single bond or $-CH_2-$, and,
- R_{17} is:
  1) H, CN, CF_3, halogen, NO_2,
  2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ or $C(=N-CN)NR_9R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5.

9. A compound according to claims 3, 4 and 5.

10. A compound according to claims 6, 7 and 8.

11. A compound as defined in claim 1 in which R1 is:

cyclohexane,
phenyl
or a bicyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is a single bond or a divalent heterocycle, and,
- R_4 is selected from:

1) H, halogen, CF_3,
2) COOH, OH,
3) $C(=O)NR_7R_8$ in which R_7 and R_8 are the same or different and are selected from H or lower alkyl,

R2 is CH_3, and,

R3 is X_2-R'_3 wherein,
- X_2 is a single bond, C_1-C_4 alkylene or C_2-C_6 alkenylene, and,
- R'3 is:

phenyl
heterocycle,
or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:
- X_3 is a single bond, and,
- R_{17} is:
  1) CN, OH, CF_3, =O, C_1-C_6 alkoxy, halogen,
  2) $COOR_5$, SO_2R_5,
  3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 or R_6,
  4) heterocycle optionally substituted with one or several groups R_5.

12. A compound as defined in any one of claims 1 to 11 in which Y is S.

13. A compound as defined in any one of claims 1 to 11 in which Y is O.

14. A compound selected from the group consisting of:
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,

(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-phenyl-ethanol,
2-{2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-ethanol,
{1-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclopentyl}-methanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
5-[5-(4-Chloro-phenyl)-3-methyl-3H[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2,5,6-trifluoro-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-propyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclobutyl-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-azepan-2-one,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclopentyl-amine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cycloheptyl-amine,
(S)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-3-methyl-butan-1-ol,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-methyl-propan-1-ol,
tert-Butyl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-isopropyl-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(1-ethyl-propyl)-amine,
4-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,

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N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,2-diamine,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-fluoro-phenyl)-amine,
N-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexane-1,4-diamine,
(1R*, 2S*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(4-trifluoromethyl-phenyl)-amine,
3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
5-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
(1-Aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenol,
(R)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-butan-1-ol,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(3-fluoro-phenyl)-amine,
(3-Chloro-phenyl)-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-acetic acid,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzamide,
Bicyclo[2.2.1]hept-2-yl-[5-(4-chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
(1R*, 2R*)-2-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
5-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-2-methoxy-phenol,
3-(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino)-benzoic acid,

3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidenoamino]-4-hydroxy-benzoic acid,
(5-Cyclohexyl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-(3-methanesulfonyl-phenyl)-amine,
(1R*, 2R*)-2-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidenoamino]-cyclohexanol,
Cyclohexyl-[5-(2,4-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(2-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[3-methyl-5-(4-trifluoromethyl-phenyl)-3*H*-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-pyridin-4-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[5-(3-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
Cyclohexyl-[5-(3-methoxy-4-nitro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
2,4-Dichloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
Cyclohexyl-(3-methyl-5-thiophen-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[5-(3,5-dichloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-[5-(2-ethyl-5-methyl-2H-pyrazol-3-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Chloro-2,6-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-(5-isoxazol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
Cyclohexyl-[3-methyl-5-(5-pyridin-2-yl-thiophen-2-yl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol,
compound with trifluoro-methanesulfonic acid
[5-(4-Chloro-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-6-methoxy-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,

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2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
2-Chloro-5-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-diethylamino-ethyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-propyl)-N-ethyl-benzenesulfonamide,
[5-(4-Chloro-phenyl)-2-cyclohexylimino-[1,3,4]thiadiazol-3-yl]-acetic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-hydroxy-ethyl)-benzamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2-diol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,6-dimethoxy-phenol,
6-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-pyridin-2-ol,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzene-1,2,3-triol,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinolin-8-ol,
Cyclohexyl-(3-methyl-5-pyrazin-2-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
5-[(E)-2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-vinyl]-2-methoxy-phenol,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol,
Cyclohexyl-(3-methyl-5-quinolin-8-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-dimethyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
[5-(5-Chloro-1H-indol-2-yl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine; compound with trifluoro-methanesulfonic acid,
2-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol; compound with 1,1,1-trifluoro-methanesulfonic acid,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol, compound with 1,1,1-trifluoro-methanesulfonic acid,
Cyclohexyl-[5-(3,4-dimethoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
[5-(3-Bromo-4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Cyclohexyl-[5-(4-methoxy-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-(3-methyl-5-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenol,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-hydroxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-*N*-(2H-tetrazol-5-yl)-benzamide hydrochloride salt,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
Cyclohexyl-{5-[4-(1-ethyl-1H-tetrazol-5-yl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isobutyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-N-methyl-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-1-(3-hydroxymethyl-piperidin-1-yl)-methanone,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester,
2-({1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-methanoyl}-amino)-3-(4-hydroxy-phenyl)-propionic acid, compound with 2,2,2-trifluoro-acetic acid,

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(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoylamino]-propionic acid, compound with 2,2,2-trifluoro-acetic acid,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyridin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-benzamide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,
N-Benzyl-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,

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4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,

(5-(4-((N-cyano-N'-ethylmorpholine)-carboximidamide)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,

Cyclohexyl-(3-methyl-5-pyridin-3-yl-3H-[1,3,4]thiadiazol-2-ylidene)-amine,

3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,

(5-Benzo[1,3]dioxol-5-yl-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene)-cyclohexyl-amine,

Cyclohexyl-[3-methyl-5-(3,4,5-trimethoxy-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,

4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,

4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

5-[5-(4-Cyano-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,

4-[4-Methyl-5-(cis-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[4-Methyl-5-(trans-4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-((1R*, 2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,

4-[5-((1R*, 2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
4-[5-((1R*, 3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzonitrile,
(1R*, 3R*))-3-[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanol,
4-[5-(1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoic acid,
4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
4-[5-((1R*, 3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide,
N-tert-Butyl-4-[5-((1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(1,1-dimethyl-3-oxo-butyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
N-(2-Cyano-1,2,2-trimethyl-ethyl)-4-[5-(1R*, 3R*)-3-hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
1-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzoylamino}-cyclopropanecarboxylic acid methyl ester,
4-(5-Cyclopentylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cycloheptylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-[5-(4-Fluoro-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,

4-[5-(3-Hydroxy-phenylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
5-[5-(4-Carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-fluoro-benzoic acid,
4-[4-Methyl-5-(4-methyl-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Bicyclo[2.2.1]hept-2-ylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2R*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,2S*)-2-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[4-Methyl-5-(3-oxo-cyclohexylimino)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(3,3-Difluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-((1R*,3R*)-3-Fluoro-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
4-[5-(Cyclohex-3-enylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-benzamide,
(1R*,3R*)-3-{3-Methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylideneamino}-cyclohexanol,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-2-hydroxy-benzoic acid,
3-[5-(4-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
2-Fluoro-5-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,

3-[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-cyclohexanecarboxylic acid,
[5-(4-methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-piperidin-1-yl amine,
[5-(4-Methanesulfonyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-(tetrahydro-pyran-4-yl)-amine,
3-[5-(4-Acetylamino-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
N-{4-[5-(trans-4-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,
N-{4-[5-((1R*,3S*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,
N-{4-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-phenyl}-acetamide,
N-{5-[5-((1R*,3R*)-3-Hydroxy-cyclohexylimino)-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-pyridin-2-yl}-acetamide,
3-[5-(4-Chloro-phenyl)-3-methyl-3H/-[1,3,4]thiadiazol-2-ylideneamino]-benzonitrile,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-N-hydroxy-benzamidine,
3-{3-[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-phenyl}-[1,2,4]oxadiazol-5-ol,
[5-(4-Bromo-3-methyl-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzonitrile,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methyl-benzamide,
[5-(4-Bromo-3-methoxy-phenyl)-3-methyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-cyclohexyl-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-hydroxy-benzamide,

4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-nitro-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Acetylamino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-1H-quinazoline-2,4-dione,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
5-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2-methoxy-benzenesulfonamide,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid methyl ester,
3-[5-(3-Cyano-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[3-Methyl-5-pyridin-2-yl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
3-[5-(4-Chloro-3-sulfamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzonitrile,
Cyclohexyl-[3-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
Cyclohexyl-[3-methyl-5-(4-nitro-phenyl)-3H-[1,3,4]thiadiazol-2-ylidene]-amine,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylamine,
[5-(4-(N-cyano-N'-(2-dimethylaminoethyl)-carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,

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N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide,
[5-(4-(bis-ethylsulfonylamino)-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(1-(2-dimethylaminoethyl)amino-2-nitro-vinylamino)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
(E)-N^1-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-2-nitro-ethene-1,1-diamine,
[5-(*N*-cyano-*N'*-methyl-4-carboximidamide-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
[5-(4-(N-cyano-N'-amino- carboximidamide)-phenyl)-3-methyl-3*H*-[1,3,4]thiadiazol-2-ylidene]-cyclohexyl-amine,
Ethanesulfonic acid [4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-amide,
[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-urea,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Chloro-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester, and,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-benzamide.

15. A compound according to claim 14, selected from the group consisting of:

5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2-methoxy-benzene-1,3-diol; compound with trifluoro-methanesulfonic acid,

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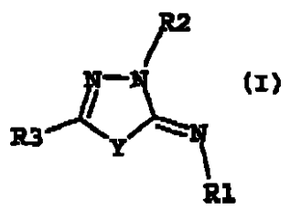
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5-(5-Cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-2,3-dimethoxy-phenol; compound with trifluoro-methanesulfonic acid,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-benzenesulfonamide,
{5-[4-Chloro-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene}-cyclohexyl-amine,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-isopropyl-N-(2-morpholin-4-yl-ethyl)-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide,
C-Chloro-(cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(dimethylamino-hydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2,3-dihydroxy-propyl)-N-ethyl-benzenesulfonamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-ethyl-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzenesulfonamide,
3-(5-Cyclohexylimino-4-methyl-4,5-dihydro-

[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-quinolin-8-yl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2,6-dimethoxy-pyridin-3-
yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-isopropyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-ethyl-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-(2-dimethylamino-ethyl)-
benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N-pyridin-4-ylmethyl-
benzamide,
2-Chloro-5-(5-cyclohexylimino-4-methyl-4,5-
dihydro[1,3,4]thiadiazol-2-yl)-N,N-diethyl-
benzenesulfonamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-methyl-benzamide,
2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-
phenyl)-propionic acid tert-butyl ester,
(S)-2-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-benzoylamino]-3-(4-hydroxy-
phenyl)-propionic acid; compound with 2,2,2-trifluoro-
acetic acid,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-(3,4,5-trimethoxy-benzyl)-
benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-[3-(4-methyl-piperazin-1-yl)-
propyl]-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-
[1,3,4]thiadiazol-2-yl)-N-pyridin-3-ylmethyl-benzamide,

N-(1-Benzyl-piperidin-4-yl)-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-ethyl-2H-pyrazol-3-yl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide,
4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide,
3-[5-(4-carbamoyl-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylideneamino]-benzoic acid,
[5-(4-Chloro-phenyl)-3-methyl-3H-[1,3,4]thiadiazol-2-ylidene]-[3-(1H-tetrazol-5-yl)-phenyl]-amine,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzoic acid methyl ester,
2-Amino-4-(5-cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-benzamide,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-3H-quinazolin-4-one,
7-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-quinazolin-4-ylamine,
N-[4-(5-Cyclohexylimino-4-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-acetamide, and,
1-[4-(Cyclohexylimino-methyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenyl]-3-(2-dimethylamino-ethyl)-urea.

16. Pharmaceutical composition comprising a compound of formula (I),



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wherein:

- Y is O or S;
- R1 is:

C_1-C_{10} alkyl,
C_2-C_{10} alkenyl,
C_2-C_{10} alkynyl,
cycloalkyl,
cycloalkenyl,
heterocycle,
aryl,
or a polycyclic group;

each optionally substituted with one or several groups X_1-R_4, identical or different, in which:

- X_1 is:
  a single bond, lower alkylene, C_2-C_6 alkanylene, cycloalkylene, arylene or a divalent heterocycle, and,
- R_4 is:
  1) H, =O, NO_2, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere,
  2) $COOR_8$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N\text{-}CN)NR_7R_8$, $C(=N\text{-}SO_2NH_2)NR_7R_8$, $C(=CH\text{-}NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_8)NHR_8$, $C(=NR_8)R_8$, $SO_2NR_7R_8$ or NR_7R_8 in which R_7 and R_8 are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH\text{-}NO_2)NR_9R_{10}$, $C(=N\text{-}SO_2NH_2)NR_9R_{10}$, $C(=N\text{-}CN)NR_9R_{10}$ or $C(=S)NR_9R_{10}$;

- R2 is:
  lower alkyl,
  C_2-C_{10} alkenyl,
  C_2-C_{10} alkynyl,
  cycloalkyl,
  cycloalkenyl,
  heterocycle,

aryl;

each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ or $NR_{11}R_{12}$ in which R_{11} and R_{12} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R3 is X_2-R'3 wherein:

- X_2 is a single bond or,

a group selected from C_1-C_4 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:

1) H, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, aryl, heterocycle, =O, CN,

2) OR_5, $=NR_5$ or,

3) $NR_{13}R_{14}$ in which R_{13} and R_{14} are the same or different and are selected from R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$;

- R'3 is:

cycloalkyl,

cycloalkenyl,

aryl,

heterocycle,

or a polycyclic group;

each optionally substituted with one or several groups X_3-R_{17}, identical or different, in which:

- X_3 is:

a single bond, lower alkylene, C_2-C_6 alkenylene, cycloalkylene, arylene, a divalent heterocycle or a divalent polycyclic group, and,

- R_{17} is:
  1) H, =O, NO_2, CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,
  2) $COOR_5$, $C(=O)R_6$, $C(=S)R_6$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,
  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ or $NR_{15}R_{16}$ in which R_{15} and R_{16} are the same or different and are selected from OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,
  4) heterocycle optionally substituted with one or several groups R_5;

wherein,

- R_5 and R_6 are the same or different and are selected from :
  - H,
  - lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
  - X_4-cycloalkyl, X_4-cycloalkenyl, X_4-aryl, X_4-heterocycle or X_4-polycyclic group, in which X_4 is a single bond, lower alkylene or C_2-C_6 alkenylene;

  each optionally substituted with one or several groups which are the same or different and which are selected from:
  - halogen, =O, $COOR_{20}$, CN, OR_{20}, lower alkyl optionally substituted with OR_{20}, O-lower alkyl optionally sustituted with OR_{20}, C(=O)-lower alkyl, lower haloalkyl, X_5-$N(R_{18})(R_{19})$ in which X_5 is a single bond or lower alkyl and R_{18}, R_{19} and R_{20} are the same or different and are selected from H or lower alkyl;
  - X_6-heterocycle, X_6-aryl, X_6-cycloalkyl, X_6-cycloalkenyl, X_6-polycyclic group in which X_6 is selected from a single bond or lower alkylene, these groups being optionally substituted with one or

several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21}, or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1 or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

- R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 or X_5-$N(R_{18})(R_{19})$ in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;
- R_{10} is selected from hydrogen, lower alkyl, cyclopropyl or heterocycle;

or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier, with the proviso that the compound of formula (I) is not 4-[2-Formylimino-5-(4-methoxy-phenyl)-[1,3,4] thiadiazol-3-yl]-butyric acid ethyl ester, or, 4-[5-(4-Chloro-phenyl)-2-formylimino-[1,3,4]thiadiazol-3-yl]-butyric acid ethyl ester.

17. A pharmaceutical composition according to claim 16, comprising a compound of formula (I), in which R1, R2, R3 and Y are as defined in claim 18, with the proviso that when R1 is C(=O)-H, then R2 does not represent $(CH2)_3$-C(=O)OCH_3CH_3.

18. Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 15, together with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition according to claim 16, 17 or 18, for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant.

20. Method for the treatment of a disease for which treatment by a PDE7 inhibitor is relevant, comprising administering to a mammal, particularly a human, in need thereof, an effective amount of compound of formula (I) according any of claims 1 to 15.

21. Method according to claim 20, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

22. Method according to claim 20, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

23. Use of a compound of formula (I) according to any one of claims 1 to 15, for the manufacture of a medicament for the treatment of diseases for which treatment by a PDE7 inhibitor is relevant.

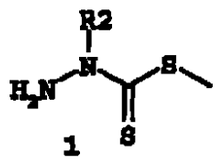
24. Use according to claim 23, in which the disease to be treated is selected from T-cell-related diseases, autoimmune diseases, inflammatory diseases, respiratory diseases, CNS diseases, allergic diseases, endocrine or exocrine pancreas diseases, or gastrointestinal diseases.

25. Use according to claim 23, in which the disease to be treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS) or graft rejection.

26. A compound of formula (I) as defined in any one of claims 1 to 15, as a medicament.

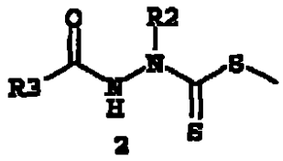
27. A process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15 in which Y is S, comprising the following steps:

(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with carbon disulphide and MeX where X is a leaving group to obtain a compound f formula 1



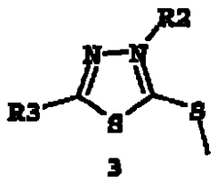
1

(b) reaction of the S-methyldithiocarbazate 1 with an acyl chloride R3COCl in which R3 is as defined in claim 1 to to obtain an acylated methyldithiocarbazate 2



2

(c) cyclization of the acylated methyldithiocarbazate 2 into a 1,3,4-thiadiazole 3



3

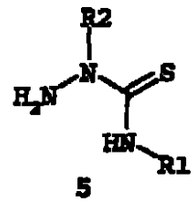
(d) reaction of the 1,3,4-thiadiazole 3 with an amine $R1NH_2$ in which R1 is as defined in claim 1, to obtain the compound of formula (I) in which Y is S,

(e) isolating the compound of formula (I).

28. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

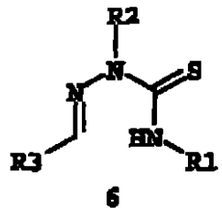
(a) reaction of a substituted hydrazine $R2NHNH_2$ in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1 in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5

AMENDED SHEET



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(b) reaction of the thiosemicarbazide 5 with an aldehyde R3CHO in which R3 is as defined in claim 1, to obtain the thiosemicarbazone 6



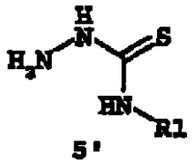
6

(c) cyclization of the thiosemicarbazone 6 into the compound of formula (I) in which Y is S,

(d) isolating the compound of formula (I).

29. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, in which Y is S, comprising the following steps:

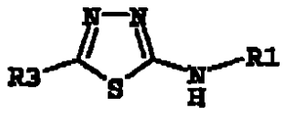
(a) reaction of a carboxylic acid R3COOH in which R3 is as defined in claim 1, with the following thiosemicarbazide 5'



5'

to obtain the 1,3,4-thiadiazole 7

AMENDED SHEET



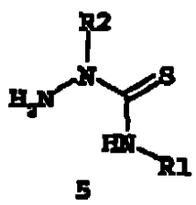
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(b) reaction of the 1,3,4-thiadiazole 7 with R2X, in which R2 is as defined in claim 1 and X is a leaving group to obtain the compound of formula (I) in which Y is S

(c) isolating the compound of formula (I).

30. Process for the preparation of a 1,3,4-thiadiazole of formula (I) according to any one of claims 1 to 12, 14 or 15, comprising the following steps:

(a) reaction of a carboxylic acid R3COOH, in which R3 is as defined in claim 1, with the following thiosemicarbazide 5



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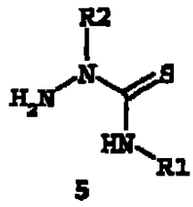
to obtain the final compound of formula I in which Y is S,

(b) isolating the compound of formula (I).

31. Process for the preparation of a 1,3,4-oxadiazole of formula (I) according to any one of claims 1 to 11 or 13, in which Y is O, comprising the following steps:

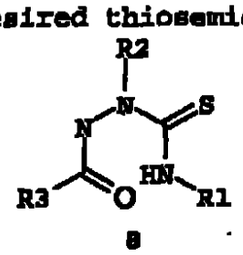
(a) reaction of a substituted hydrazine $R2NHNH_2$, in which R2 is as defined in claim 1, with a substituted isothiocyanate SCNR1, in which R1 is as defined in claim 1, to obtain the substituted thiosemicarbazide 5,

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(b) reaction of the thiosemicarbazide 5 with R3-C(=O)Cl, in which R3 is as defined in claim 1, to form the desired thiosemicarbazide 8



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(c) cyclization of the thiosemicarbazide 8 into the final compound of formula I in which Y is O,

(d) isolating the compound of formula (I).

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TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT. NOTIFICACION DE REMISIÓN DEL INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL (PCT, Norma 71.1)

De la: AUTORIDAD DE EXAMEN PRELIMINAR INTERNACIONAL

Para:

Hirsch, Denise

WARNER-LAMBERT COMPANY

c/o PARKE-DAVIS

Pfizer Global Research & Development, Fresnes Laboratories

3-9 rue de la Loge, B.P. 100

F-94265 Fresnes

FRANCIA

[aparece sello que reza:] Recibido el 13 de enero de 2003, Patentes. Fresnes

Fecha de envío *(día/mes/año)*: 10.01.2003

Referencia de archivo del solicitante o agente: 018155-A305

NOTIFICACIÓN IMPORTANTE

Solicitud internacional número: PCT/EP01/11330

Fecha de presentación internacional *(día/mes/año)*: 01/10/2001

Fecha de prioridad *(día/mes/año)*: 02/10/2000

Solicitante: WARNER-LAMBERT COMPANY

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1. Por la presente se notifica al solicitante que esta Autoridad de Examen Preliminar Internacional remite por la presente el informe del examen preliminar internacional y sus anexos, si los hubiere, establecido sobre la solicitud internacional.

2. Se remite una copia del informe y sus anexos, si hubiere, a la Oficina Internacional para su comunicación a las Oficinas elegidas.

3. Cuando las Oficinas elegidas así lo soliciten, la Oficina Internacional preparará una traducción al inglés del informe (pero no de sus anexos) y la remitirá a dichas Oficinas.

4. RECORDATORIO:

El solicitante debe ingresar en la fase nacional ante cada una de las Oficinas elegidas realizando ciertos trámites (presentación de traducciones y pago de aranceles nacionales) dentro de los 30 meses contados desde la fecha de prioridad (o más tarde en algunas Oficinas) (Cláusula 39(1)) (véase también el recordatorio enviado por la Oficina Internacional con el Formulario PCT/IB/301).

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Cuando deba presentarse una traducción de la solicitud internacional ante una Oficina elegida, dicha traducción deberá incluir la traducción de todos los anexos al informe del examen preliminar internacional. La preparación y presentación de la traducción directamente ante cada Oficina elegida es responsabilidad del solicitante.

Para obtener más detalles sobre los plazos aplicables y requisitos de las Oficinas elegidas, véase el Volumen II de la Guía para el Solicitante por PCT.

Con el fin de decidir si la invención que se reivindica es patentable o no, las Oficinas elegidas pueden solicitar un criterio adicional o diferente del criterio sobre el que se fundamenta el informe de examen preliminar internacional (véase Cláusulas 27(5), 33(5). Entre los criterios adicionales puede encontrarse, por ejemplo, exenciones de patentabilidad y los requisitos de permitir la revelación y los de claridad y sustento de las reivindicaciones.

Nombre y domicilio para correspondencia de la IPEA/
Oficina de Patentes Europea- P.B. 5818 Patentlaan 2
NL-2280 HV Rijwijk-Pays Bas
Tel. + 31 70 340-2040 Tx: 31 651 epo nl
Fax: +31 70 340-3016

61362 346

Funcionario autorizado:

Smith, K

Tel. +31 70 340-3479

[aparece un sello en un tercer idioma]

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TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

(PCT, Cláusula 36 y Norma 70)

Referencia de archivo del solicitante o agente: 018155-A305

PARA OTROS TRÁMITES: Véase la Notificación de Remisión del Informe de Examen Preliminar Internacional (Formulario PCT/IPEA/416)

Solicitud internacional No.: PCT/EP01/11330

Fecha de Presentación Internacional (*día/mes/año*): 01/10/2001

Fecha de prioridad (*día/mes/año*): 02/10/2000

Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC

C07D285/135

Solicitante: WARNER-LAMBERT COMPANY

1. Este informe de examen preliminar internacional ha sido preparado por la Autoridad de Examen Preliminar Internacional y se remite al solicitante conforme a la Cláusula 36.

2. El INFORME se compone de un total de 6 páginas, incluyendo esta carátula.

[x] Este informe se encuentra acompañado también con ANEXOS, es decir, páginas de la memoria descriptiva, reivindicaciones y/o dibujos que se han modificado y constituyen la base de este informe y/o páginas que contienen rectificaciones hechas ante esta Autoridad (véase la Norma 70.16 y el Artículo 607 de las Instrucciones Administrativas conforme al PCT).

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Estos anexos constan de 70 páginas.

3. Este informe contiene indicaciones relacionadas con los siguientes puntos:

I. [x] Fundamento del informe

II.[ ] Prioridad

III.[X] No establecimiento de opinión sobre la novedad, paso inventivo y aplicación industrial.

IV. [ ] Falta de unidad de invención

V. [x] Declaración fundamentada conforme a la Cláusula 35(2) sobre la novedad, paso inventivo o aplicación industrial; citas y explicaciones que fundamentan dicha declaración.

VI. [ ] Ciertos documentos citados

VII. [ ] Ciertos defectos en la solicitud internacional

VIII.[ ] Ciertas observaciones sobre la solicitud internacional

Fecha de presentación del pedido: 26/04/2002

Fecha de finalización del informe: 10.01.2003

Nombre y domicilio para correspondencia de la autoridad de examen preliminar internacional:

Oficina de Patentes Europea- P.B. 5818 Patentlaan 2

NL-2280 HV Rijwijk-Pays Bas

Tel. + 31 70 340-2040 Tx: 31 651 epo nl

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Tel. +31 70 340-2002

[aparece un sello en un tercer idioma]

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INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No.PCT/EP01/11330

I. Fundamento del informe

1. Con respecto a los **elementos** de la solicitud internacional (*Las páginas reemplazantes que se han presentado ante la Oficina Receptora en respuesta a una invitación conforme a la Cláusula 14, se denominan en este informe "originalmente presentadas" y no se anexan a este informe ya que no contienen modificaciones (Normas 70.16 y 70.17))*:

Memoria descriptiva, páginas:

1-200 originalmente presentadas

Reivindicaciones, No.:

1-31 como se recibieron el 05/12/2002 con la carta del 05/12/2002

2. Con respecto al **idioma**, todos los elementos marcados anteriormente estuvieron disponibles o fueron presentadas ante esta Autoridad en el idioma en el cual se presentó la solicitud internacional, a menos que se indique lo contrario en este punto.

Estos elementos estuvieron disponibles o fueron presentados ante esta Autoridad en el siguiente idioma: , que es:

[ ] el idioma de la traducción presentada para los propósitos de la búsqueda internacional (conforme a la Norma 23.1(b)).

[ ] el idioma de la publicación de la solicitud internacional (conforme a la Norma 48.3(b)).

[ ] el idioma de la traducción presentada para los propósitos del examen preliminar internacional (conforme a la Norma 55.2 y/o 55.3).

3. Con respecto a cualquier **secuencia de nucleótidos y/o aminoácidos** revelada en la solicitud internacional, el examen preliminar internacional se realizó sobre la base del listado de secuencias:

[ ] contenido en la solicitud internacional en forma escrita

[ ] presentado junto con la solicitud internacional en forma legible por computadora

[ ] presentado con posterioridad ante esta Autoridad en forma escrita

[ ] presentado con posterioridad ante esta Autoridad en forma legible por computadora

[ ] La declaración de que el listado de secuencias escrito presentado con posterioridad no va más allá de la revelación de la solicitud internacional presentada ha sido presentada.

[ ] La declaración de que la información registrada en forma legible por computadora es idéntica al listado de secuencias escrito ha sido presentada.

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4. Las enmiendas han dado lugar a la cancelación de:

[ ] la memoria descriptiva, páginas:

[ ] las reivindicaciones, Nos.:

[ ] los dibujos, láminas:

5. [] Este informe se ha establecido como si (algunas de) las enmiendas no se hubieran introducido, ya que se ha considerado que éstas exceden la invención presentada (Norma 70.2(c)).

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INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional N°: PCT/EP01/11330

(Todas las páginas de reemplazo que contengan dichas enmiendas se deben en el punto 1 y anexar a este informe.)

6. Observaciones adicionales, si fuera necesario:

III. No establecimiento de opinión con respecto a la novedad, al paso inventivo y a la aplicación industrial

1. Las cuestiones sobre si la invención reivindicada parece ser novedosa, involucrar un paso inventivo (no ser obvia), o ser aplicable industrialmente no han sido examinadas con respecto a:

[ ] la solicitud internacional completa,

[x] las reivindicaciones Nos. 20-22.

porque:

[x] la solicitud internacional, o las reivindicaciones Nos. 20-22 se relacionan con el siguiente objeto que no requiere un examen preliminar internacional (*especificar*):

ver la página aparte

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[ ] la memoria descriptiva, las reivindicaciones o los dibujos (indicar los elementos particulares abajo) o las reivindicaciones Nos. son tan poco claras que no se puede formar ninguna opinión significativa (*especificar*):

[ ] las reivindicaciones, o las reivindicaciones Nos. están tan inadecuadamente sustentadas por la memoria descriptiva que no se puede formar ninguna opinión significativa.

[ ] no se ha establecido ningún informe de búsqueda internacional para las reivindicaciones Nos.

2. No se puede emitir una opinión escrita debido a que el listado de secuencias de nucleótidos y/o aminoácidos no cumple con la norma establecida en el Anexo C de las instrucciones administrativas:

[ ] la forma escrita no ha sido presentada o no cumple con la norma

[ ] la forma legible por computadora no ha sido presentada o no cumple con la norma.

V. Declaración fundamentada conforme a la Cláusula 35(2) sobre la novedad, paso inventivo o aplicación industrial, citas y explicaciones que fundamentan dicha declaración.

1. Declaración

Novedad (N)	SI:	Reivindicaciones	1-31
	NO:	Reivindicaciones	-
Paso Inventivo (IS)	SI:	Reivindicaciones	1-31
	NO:	Reivindicaciones	-
Aplicación industrial (IA)	SI:	Reivindicaciones	1-19, 23-31

INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional N°: PCT/EP01/11330

NO: Reivindicaciones: -

2. Citas y explicaciones

véase página aparte

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INFORME DE EXAMEN PRELIMINAR INTERNACIONAL-PÁGINA APARTE

Solicitud internacional No. PCT/EP01/11330

Se hace referencia al siguiente documento:

D6: WO 99 42089 A (ROCHE DIAGNOSTICS GMBH) 26 de agosto de 1999 (1999-08-26)

Re al punto III

No establecimiento de opinión con respecto a la novedad, el paso inventivo y la aplicación industrial.

Las reivindicaciones 20-22 se refieren a un objeto que esta Autoridad considera cubierto por las disposiciones de la Norma 67.1(iv) del PCT. Por lo tanto, no se formulará opinión con respecto a la aplicación industrial del objeto de estas reivindicaciones (Cláusula 34(4)(a)(I) del PCT).

Para la evaluación de las presentes reivindicaciones 20-22 sobre la cuestión de si son aplicables industrialmente, no existen criterios unificados en los Estados Firmantes del PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como aplicable industrialmente el objeto de las reivindicaciones en cuanto al uso de un compuesto en un tratamiento médico, pero puede admitir, sin embargo, reivindicaciones de un compuesto

conocido para el primer uso en un tratamiento médico y el uso de tal compuesto para la fabricación de un medicamento para un nuevo tratamiento médico.

Re al punto V

Declaración fundamentada conforme a la Cláusula 35(2) sobre la novedad, paso inventivo o aplicación industrial, citas y explicaciones que fundamentan dicha declaración

Novedad (cláusula 33(2) del PCT)

Ni los compuestos de acuerdo con la reivindicación 1 ni las composiciones farmacéuticas de acuerdo con la reivindicación 16 se revelan en el arte previo disponible; por lo tanto, el objeto de las reivindicaciones 1-31 es novedoso.

Solicitud internacional No. PCT/EP01/11330

Paso inventivo (Cláusula 33(3) PCT)

En vista de las enseñanzas que aporta D6, el cual se considera que representa el arte previo más cercano y describe imino-tiadiazolpiridinas útiles como inhibidoras de la fosfodiesterasa, el problema que subyace y se resuelve en la presente solicitud puede verse en el suministro de otros compuestos imino-heterocíclicos con la misma actividad.

La solución a este problema planteada por la presente solicitud, esto es, los compuestos de acuerdo con la reivindicación 1 o las composiciones de acuerdo con la reivindicación 16, no se indica en el arte previo disponible; por lo tanto el objeto de las reivindicaciones 1-31 tiene paso inventivo.

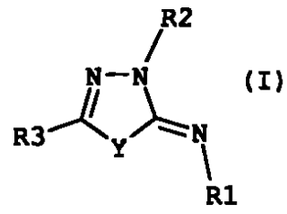
Aplicación industrial (Cláusula 33(4) del PCT

Los compuestos, composiciones y métodos de las reivindicaciones 1-19 y 23-31 pueden utilizarse en la industria farmacéutica.

REIVINDICACIONES

Habiendo descrito y determinado la naturaleza y alcance de la presente invención y la manera en que la misma ha de ser llevada a la práctica, se declara que lo que reivindica como invención y de propiedad exclusiva es:

1. Un compuesto que tiene la siguiente fórmula (I),



en donde

- Y es O o S;
- R_1 es:

  alquilo de C_4-C_{10},

  alquenilo de C_2-C_{10},

  alquinilo de C_2-C_{10},

  cicloalquilo,

  cicloalquenilo,

  heterociclo,

  arilo,

  o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4,

idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y,

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_4-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es $X_2-R'_3$ en donde:

- X_2 es un solo enlace o,

un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y

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se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo policíclico divalente, y,

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o

$NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenileno de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-$\underset{R_{19}}{N}$-R_{18} en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policíclico en donde X_6 se

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selecciona de un solo enlace o alquileno inferior, estos grupos se sustituyen optativamente con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o X_5-N-R_{18} en donde R_{19} X_5 es un

solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

con la condición de que,

- cuando R_1 es fenilo, lleva por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y tanto R_1 como R'_3 son fenilo, cada uno de R_1 y R'_3 llevan por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y R'_3 es fenilo, R'_3 no se sustituye con un éster o un ácido carboxílico en la posición orto,

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- cuando R_3 representa un fenilo sustituido e Y representa O, entonces R_1 es diferente de 1,3,5-triazina sustituida,

- el átomo de R_3 que está unido al grupo tiadiazol es un átomo de carbono,

excluyendo los siguientes compuestos,

(3,5-difenil-3H-[1,3,4]oxadiazol-2-iliden)-naftalen-2-il-amina,

terc-butil-(3-terc-butil-5-fenil-3H-[1,3,4]oxadiazol-2-iliden)-amina,

dietil éster del ácido 2-[(3-metil-5-fenil-3H-[1,3,4]oxadiazol-2-ilidenamino)-metilen]-malónico,

[4-(4-metoxi-fenil)-5-(4-metoxi-fenilamino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]fenil-metanona,

(4-metoxi-fenil)-[4-(4-metoxi-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-metanona,

[4-(4-fluoro-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-fenil-metanona,

1-Fenil-1-[4-fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-metanona,

1-[4-Fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-1-tiofen-2-il-metanona,

1-Fenil-1-(4-fenil-5-*p*-tolilimino-4,5-dihidro-[1,3,4]tiadiazol-2-il)-metanona,

Ciclohexil-[3-(2,4,6-tricloro-fenil)-5-(2,3,3-trimetil-ciclopent-1-enilmetil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

2-(3,5-Difenil-3*H*-[1,3,4]tiadiazol-2-ilidenamino)-1,4-difenil-

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but-2-en-1,4-diona,

Dimetil éster del ácido 2-[3-Fenil-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico,

Dimetil éster del ácido 2-[5-(1-Fenil-metanoil)-3-*p*-tolil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico, y,

Dimetil éster del ácido 2-[3-(4-Cloro-fenil)-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico.

2. Un compuesto de acuerdo con la reivindicación 1, en donde R_1, R_2, R_3 e Y son lo definido en la reivindicación 1 con la condición de que, cuando R_2 es fenilo, no sustituido o sustituido con 1 a 3 cloro o con un metilo, entonces R_3 no representa C(=O)-fenilo, C(=O)-tienilo, fenilo o CH_2-(2,3,3-trimetil-ciclopent-1-enilo).

3. Un compuesto de la fórmula (I) definido en la reivindicación 1 o 2, en donde porque R_1 es:

alquilo de C_4-C_6,

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es un solo enlace, un heterociclo divalente o un alquileno inferior, y

- R_4 se selecciona de:

1) H, =O, halógeno, CN, haloalquilo inferior, preferentemente CF_3, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=S)NR_9R_{10}$,

en donde R_5 se selecciona de hidrógeno o alquilo inferior, optativamente sustituido con OH, y R_6, R_9 y R_{10} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior.

4. Un compuesto definido en cualquiera de las reivindicaciones 1 a 3, en donde R_2 es alquilo inferior.

5. Un compuesto definido en cualquiera de las reivindicaciones 1 a 4, en donde R_3 es X_2-R'_3 en donde

- X_2 es solo enlace, alquileno de C_1-C_4, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, y

- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico,

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o alquileno inferior, y
- R_{17} es:

  1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

  2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

  3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

  4) heterociclo optativamente sustituido con uno o varios grupos R_5.

6. Un compuesto definido en cualquiera de las reivindicaciones 1 a 5, en donde R_1 es:

cicloalquilo, preferentemente ciclohexano,

cicloalquenilo,

arilo, preferentemente fenilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferente, en donde:

- X_1 es solo enlace o un heterociclo divalente y,
- R_4 se selecciona de:

1) H, halógeno, CF_3, =O,

2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$.

en donde R_5 y R_6 son idénticos o diferentes y se seleccionan de hidrógeno o metilo.

7. Un compuesto definido en cualquiera de las reivindicaciones 1 a 6, en donde R_2 es CH_3.

8. Un compuesto definido en cualquiera de las reivindicaciones 1 a 7, en donde R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6, y

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- R'_3 es:

cicloalquilo,

arilo, preferentemente fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o $-CH_2-$, y

- R_{17} es:

1) H, CN, CF_3, halógeno, NO_2,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=N-CN)NR_9R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

9. Un compuesto de acuerdo con las reivindicaciones 3, 4, y 5.

10. Un compuesto de acuerdo con las reivindicaciones 6, 7 y 8.

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11. Un compuesto definido en la reivindicación 1, en donde R_1 es:

ciclohexano,

fenilo

o un grupo bicíclico;

cada uno optativamente susituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es solo enlace o un heterociclo divalente, y

- R_4 se selecciona de:

1) H, halógeno, CF_3,

2) COOH, OH,

3) $C(=O)NR_7R_8$ en donde R_7 y R_8 son iguales o diferentes y se seleccionan de H o alquilo inferior,

R_2 es CH_3, y

R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6 y

- R'_3 es:

fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

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- X_3 es un solo enlace, y

- R_{17} es:

1) CN, OH, CF_3, =O, alcoxi de C_1-C_6, halógeno,

2) $COOR_5$, SO_2R_5,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 o R_6,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

12. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es S.

13. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es O.

14. Un compuesto seleccionado del grupo formado por:
Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,
Ácido (1R*, 2R*)-2-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,
(S)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fenil-etanol,

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2-{2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-etanol,

{1-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclopentil}-metanol,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2,5,6-trifluoro-benzoico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-propil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclobutil-amina,

3-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-azepan-2-ona,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclopentil-amina,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-cicloheptil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-3-metil-butan-1-ol,

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2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-metil-propan-1-ol,

terc-Butil-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-isopropil-amina,

Ácido 4-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(1-etil-propil)-amina,

4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,2-diamina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-fluoro-fenil)-amina,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,4-diamina,

(1R*, 2S*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-trifluorometil-fenil)-amina,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

(1-Aza-biciclo[2.2.2]oct-3-il)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

(R)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-fluoro-fenil)-amina,

(3-Cloro-fenil)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ácido {3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-acético,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzamida,

Biciclo[2.2.1]hept-2-il-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

(1R*, 2R*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

5-(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-2-metoxi-fenol,

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Ácido 3-(5-ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-4-hidroxi-benzoico,

(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-(3-metanosulfonil-fenil)-amina,

(1R*,2R*)-2-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ciclohexil-[5-(2,4-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(2-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[3-metil-5-(4-trifluorometil-fenil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-piridin-4-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[5-(3-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

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Ciclohexil-[5-(3-metoxi-4-nitro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2,4-Dicloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Ciclohexil-(3-metil-5-tiofen-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[5-(3,5-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-[5-(2-etil-5-metil-2H-pirazol-3-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Cloro-2,6-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-(5-isoxazol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[3-metil-5-(5-piridin-2-il-tiofen-2-il)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

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2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-6-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

2-Cloro-5-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dietilamino-etil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-propil)-N-etil-bencenosulfonamida,

Metil éster del ácido [5-(4-Cloro-fenil)-2-ciclohexilimino-[1,3,4]tiadiazol-3-il]-acético,

Metil éster del ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-hidroxi-etil)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2-diol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,6-dimetoxi-fenol,

6-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-piridin-2-ol,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2,3-triol,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinolin-8-ol,

Ciclohexil-(3-metil-5-pirazin-2-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

5-[(E)-2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-vinil]-2-metoxi-fenol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol,

Ciclohexil-(3-metil-5-quinolin-8-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

4-(5-Ciclohexilimino-4-methyl-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

[5-(5-Cloro-1H-indol-2-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina; compuesto con ácido trifluoro-metanesulfónico,

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2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

Ciclohexil-[5-(3,4-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Bromo-4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[5-(4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-fenil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-hidroxi-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Sal de clorhidrato de 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-*N*-(2H-tetrazol-5-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

Ciclohexil-{5-[4-(1-etil-1H-tetrazol-5-il)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isobutil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

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4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-N-metil-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-1-(3-hidroximetil-piperidin-1-il)-metanona,

terc-Butil éster del ácido 2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido 2-({1-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-metanoil}-amino)-3-(4-hidroxi-fenil)-propiónico, compuesto con ácido 2,2,2-trifluoro-acético,

terc-Butil éster del ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido (S)-2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-piridin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-[4-(4-fluoro-fenil)-piperazin-1-il]-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-pirimidin-2-il-piperazin-1-il)-metanona,

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[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-metil-piperazin-1-il)-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(1-etil-pirrolidin-2-ilmetil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-Bencil-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-1)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

[5-(4-((N-ciano-N'-etilmorfolin)-carboximidamido)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

Ciclohexil-(3-metil-5-piridin-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

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(5-Benzo[1,3]dioxol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-ciclohexil-amina,

Ciclohexil-[3-metil-5-(3,4,5-trimetoxi-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

Ácido 5-[5-(4-Ciano-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(cis-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[4-Metil-5-(trans-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

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4-[5-((1R*, 2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

(1R*, 3R*))-3-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ácido 4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-morfolin-4-il-etil)-benzamida,

Ácido 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

N-terc-Butil-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(1,1-dimetil-3-oxo-butil)-4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(2-Ciano-1,2,2-trimetil-etil)-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Metil éster del ácido 1-{4-[5-((1R*,3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoilamino}-ciclopropanocarboxílico,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-benzamida,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Ácido 5-[5-(4-Carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

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4-[5-((1R*,2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[4-Metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3,3-Difluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Fluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

(1R*,3R*)-3-{3-Metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-ilidenamino}-ciclohexanol,

Ácido 3-[5-(4-cloro-fenyl)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

Ácido 3-[5-(4-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 2-fluoro-5-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-piperidin-1-il amina,

[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(tetrahidro-piran-4-il)-amina,

Ácido 3-[5-(4-acetilamino-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

N-{4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{5-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-piridin-2-il}-acetamida,

3-[5-(4-Cloro-fenil)-3-metil-3H/-[1,3,4]tiadiazol-2-ilidenamino]-benzonitrilo,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-N-hidroxi-benzamidina,

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3-{3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-metil-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzonitrilo,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzamida,

[5-(4-Bromo-3-metoxi-fenil)-3-metil-2,3-dihidro-[1,3,4]tiadiazol-2-il]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-hidroxi-benzamida,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-nitro-benzoico,

Metil éster del ácido 2-amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Metil éster del ácido 2-acetilamino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

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7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-1H-quinazolin-2,4-diona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

Metil éster del ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[3-metil-5-piridin-2-il-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-Cloro-3-sulfamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-{3-metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-iliden}-amina,

Ciclohexil-[3-metil-5-(4-nitro-fenil)-3H-[1,3,4] tiadiazol-2-iliden]-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenilamina,

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[5-(4-(N-ciano-N'-(2-dimetilaminoetil)-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida,

[5-(4-(bis-etilsulfonilamino)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(1-(2-dimetilaminoetil)amino-2-nitro-vinilamino)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

(E)-N^1-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-2-nitro-eten-1,1-diamina,

[5-(*N*-ciano-*N'*-metil-4-carboximidamido-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(N-ciano-N'-amino-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-amida del ácido etanosulfónico,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-fenil]-urea,

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Metil éster del ácido 2-cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

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2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Metil éster del ácido 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzoico y

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzamida

15. Un compuesto de acuerdo con la reivindicación 14, seleccionado del grupo formado por:

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

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2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

terc-butil éster del ácido 2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

metil éster del ácido 2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

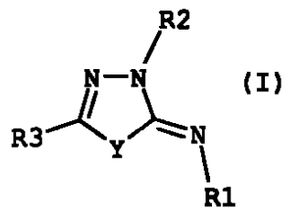
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7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida, y

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea.

16. Una composición farmacéutica que comprende un compuesto de la fórmula (I)



en donde:

- Y es O o S;
- R_1 es:

alquilo de C_1-C_{10},

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior,

halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es $X_2-R'_3$ en donde:

- X_2 es un solo enlace o,

un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

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cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo heterocíclico divalente, y

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, bioisóstero de ácido carboxílico, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

en donde,

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenilo de C_2-C_6;

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cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, $X_5-N(R_{19})-R_{18}$

en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policiclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos optativamente se sustituyen con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o $X_5-N(R_{19})-R_{18}$ en donde X_5 es un

solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

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junto con un portador farmacéuticamente aceptable,
con la condición de que el compuesto de la fórmula (I) no sea etil éster del ácido 4-[2-Formilimino-5-(4-metoxi-fenil)-[1,3,4] tiadiazol-3-il]-butírico, o
etil éster del ácido 4-[5-(4-cloro-fenil)-2-formilimino-[1,3,4]tiadiazol-3-il]-butírico.

17. Una composición farmacéutica de acuerdo con la reivindicación 16, que comprende un compuesto de la fórmula (I), en donde R_1, R_2, R_3 e Y son lo definico en la reivindicación 18, con la condición de que cuando R_1 es C(=O)-H, R_2 no represente $(CH_2)_3$-C(=O)OCH_2CH_3.

18. Una composición farmacéutica que comprende un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, junto con un portador farmacéuticamente aceptable.

19. Una composición farmacéutica de acuerdo con la reivindicación 16, 17 o 18, para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante.

20. Un método para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante, que

comprende administrar a un mamífero, particularmente a un humano, que lo necesita, una cantidad eficaz de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15.

21. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se debe tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

22. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

24. El uso de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, para la fabricación de un medicamento para el tratamiento de enfermedades para las cuales el tratamiento con un inhibidor de PDE7 es relevante.

24. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

25. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

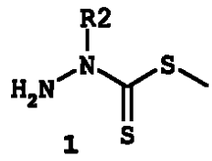
26. Un compuesto de la fórmula (I), definido en cualquiera de las reivindicaciones 1 a 15, como medicamento.

27. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reividindicación 1, con disulfuro de

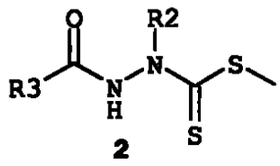
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carbono y MeX donde X es un grupo saliente para obtener un compuesto de la fórmula 1



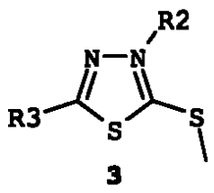
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(b) reacción del S-metilditiocarbazato 1 con un cloruro de acilo R_3COCl en donde R_3 es lo definido en la reivindicación 1 para obtener un metilditiocarbazato acilado 2



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(c) ciclación del metilditiocarbazato acilado 2 en un 1,3,4-tiadiazol 3



3

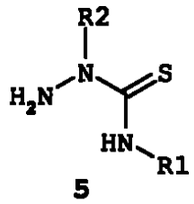
(d) reacción del 1,3,4-tiadiazol 3 con una amina R_1NH_2 en donde R_1 es lo definido en reivindicación 1, para obtener el compuesto de la fórmula (I) en donde Y es S,

(e) aislación del compuesto de la fórmula (I).

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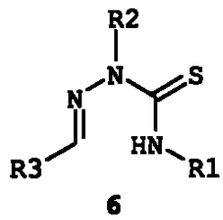
28. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$ en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5



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(b) reacción de la tiosemicarbazida 5 con un aldehído R_3CHO en donde R_3 es lo definido en la reivindicación 1, para obtener la tiosemicarbazona 6



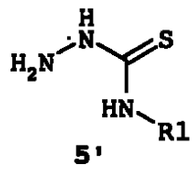
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(c) ciclación de la tiosemicarbazona 6 en el compuesto de la fórmula (I) en donde Y es S,

(d) aislación del compuesto de la fórmula (I).

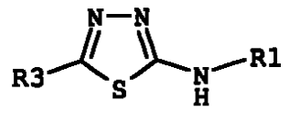
29. El proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de un ácido carboxílico R_3COOH en donde R_3 es lo definido en reivindicación 1, con la siguiente tiosemicarbazida 5'



5'

para obtener el 1,3,4-tiadiazol 7



7

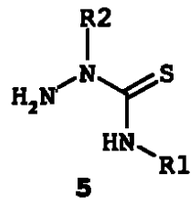
(b) reacción del 1,3,4-tiadiazol 7 con R_2X, en donde R_2 es lo definido en la reivindicación 1 y X es un grupo saliente para obtener el compuesto de la fórmula (I) en donde Y es S

(c) aislación del compuesto de la fórmula (I).

30. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 14, que comprende los siguientes pasos:

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(a) reacción de un ácido carboxílico R_3COOH, en donde R_3 es lo definido en la reivindicación 1, con la siguiente tiosemicarbazida 5



5

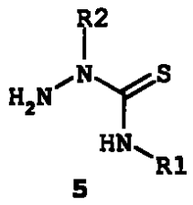
para obtener el compuesto final de la fórmula I en donde Y es S,

(b) aislación del compuesto de la fórmula (I).

31. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 11 o 13, en donde Y es S, que comprende los siguientes pasos:

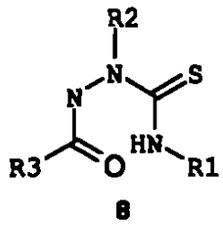
(a) reacción de una hidrazina sustituida R_2NHNH_2, en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$, en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5,

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5

(b) reacción de la tiosemicarbazida 5 con R_3-C(=O)Cl, en donde R_3 es lo definido en la reivindicación 1, para formar la tiosemicarbazida 8 deseada



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(c) ciclación de la tiosemicarbazida 8 en el compuesto final de la fórmula I en donde Y es O,

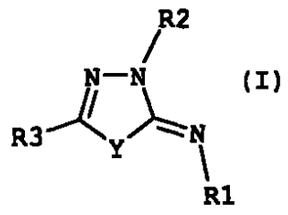
(d) aislación del compuesto de la fórmula (I).

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REIVINDICACIONES

1. Un compuesto que tiene la siguiente fórmula (I),



en donde

- Y es O o S;
- R_1 es:

  alquilo de C_4-C_{10},

  alquenilo de C_2-C_{10},

  alquinilo de C_2-C_{10},

  cicloalquilo,

  cicloalquenilo,

  heterociclo,

  arilo,

  o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4,

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idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y,

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_4-C_{10},

cicloalquilo,

cicloalquenilo,

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heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior, halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es $X_2-R'_3$ en donde:

- X_2 es un solo enlace o,

un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y

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se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo policíclico divalente, y,

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o

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$NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenileno de C_2-C_6;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-$\underset{R_{19}}{N}$-R_{18} en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policíclico en donde X_6 se

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selecciona de un solo enlace o alquileno inferior, estos grupos se sustituyen optativamente con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o X_5-N-R_{18} en donde R_{19} X_5 es un

solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

con la condición de que,

- cuando R_1 es fenilo, lleva por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y tanto R_1 como R'_3 son fenilo, cada uno de R_1 y R'_3 llevan por lo menos un sustituyente que no es H,

- cuando X_2 es un solo enlace y R'_3 es fenilo, R'_3 no se sustituye con un éster o un ácido carboxílico en la posición orto,

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- cuando Y representa O y R_3 representa un fenilo o un cicloalquilo, no sustitudo o sustituido, entonces R_1 es diferente de 1,3,5-triazina sustituida,
- el átomo de R_3 que está unido al grupo tiadiazol es un átomo de carbono,

excluyendo los siguientes compuestos,

(3,5-difenil-3H-[1,3,4]oxadiazol-2-iliden)-naftalen-2-il-amina,

terc-butil-(3-terc-butil-5-fenil-3H-[1,3,4]oxadiazol-2-iliden)-amina,

dietil éster del ácido 2-[(3-metil-5-fenil-3H-[1,3,4]oxadiazol-2-ilidenamino)-metilen]-malónico,

[4-(4-metoxi-fenil)-5-(4-metoxi-fenilamino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]fenil-metanona,

(4-metoxi-fenil)-[4-(4-metoxi-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-metanona,

[4-(4-fluoro-fenil)-5-(4-metoxi-fenilimino)-4,5-dihidro-[1,3,4]oxadiazol-2-il]-fenil-metanona,

1-Fenil-1-[4-fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-metanona,

1-[4-Fenil-5-(5-trifluorometil-2*H*-[1,2,4]triazol-3-ilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-1-tiofen-2-il-metanona,

1-Fenil-1-(4-fenil-5-*p*-tolilimino-4,5-dihidro-[1,3,4]tiadiazol-2-il)-metanona,

Ciclohexil-[3-(2,4,6-tricloro-fenil)-5-(2,3,3-trimetil-ciclopent-1-enilmetil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

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2-(3,5-Difenil-3*H*-[1,3,4]tiadiazol-2-ilidenamino)-1,4-difenil-but-2-en-1,4-diona,

Dimetil éster del ácido 2-[3-Fenil-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico,

Dimetil éster del ácido 2-[5-(1-Fenil-metanoil)-3-*p*-tolil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico, y,

Dimetil éster del ácido 2-[3-(4-Cloro-fenil)-5-(1-fenil-metanoil)-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-but-2-endioico.

2. Un compuesto de acuerdo con la reivindicación 1, en donde R_1, R_2, R_3 e Y son lo definido en la reivindicación 1 con la condición de que, cuando R_2 es fenilo, no sustituido o sustituido con 1 a 3 cloro o con un metilo, entonces R_3 no representa C(=O)-fenilo, C(=O)-tienilo, fenilo o CH_2-(2,3,3-trimetil-ciclopent-1-enilo).

3. Un compuesto de la fórmula (I) definido en la reivindicación 1 o 2, en donde porque R_1 es:

alquilo de C_4-C_6,

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4,

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idénticos o diferentes, en donde:

- X_1 es un solo enlace, un heterociclo divalente o un alquileno inferior, y
- R_4 se selecciona de:

1) H, =O, halógeno, CN, haloalquilo inferior, preferentemente CF_3, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$

3) $C(=O)NR_7R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=S)NR_9R_{10}$,

en donde R_5 se selecciona de hidrógeno o alquilo inferior, optativamente sustituido con OH, y R_6, R_9 y R_{10} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior.

4. Un compuesto definido en cualquiera de las reivindicaciones 1 a 3, en donde R_2 es alquilo inferior.

5. Un compuesto definido en cualquiera de las reivindicaciones 1 a 4, en donde R_3 es X_2-R'_3 en donde

- X_2 es solo enlace, alquileno de C_1-C_4, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, y

- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico,

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o alquileno inferior, y

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

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6. Un compuesto definido en cualquiera de las reivindicaciones 1 a 5, en donde R_1 es:

cicloalquilo, preferentemente ciclohexano,

cicloalquenilo,

arilo, preferentemente fenilo,

o un grupo bicíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferente, en donde:

- X_1 es solo enlace o un heterociclo divalente y,
- R_4 se selecciona de:

1) H, halógeno, CF_3, =O,

2) $COOR_5$, OR_5,

3) $C(=O)NR_5R_6$.

en donde R_5 y R_6 son idénticos o diferentes y se seleccionan de hidrógeno o metilo.

7. Un compuesto definido en cualquiera de las reivindicaciones 1 a 6, en donde R_2 es CH_3.

8. Un compuesto definido en cualquiera de las reivindicaciones 1 a 7, en donde R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6, y

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- R'_3 es:

cicloalquilo,

arilo, preferentemente fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es un solo enlace o $-CH_2-$, y

- R_{17} es:

1) H, CN, CF_3, halógeno, NO_2,

2) $COOR_5$, SO_2R_5, OR_5, $C(=O)R_5$,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$ o $C(=N-CN)NR_9R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

9. Un compuesto de acuerdo con las reivindicaciones 3, 4, y 5.

10. Un compuesto de acuerdo con las reivindicaciones 6, 7 y 8.

11. Un compuesto definido en la reivindicación 1, en donde R_1 es:

ciclohexano,

fenilo

o un grupo bicíclico;

cada uno optativamente susituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es solo enlace o un heterociclo divalente, y
- R_4 se selecciona de:

1) H, halógeno, CF_3,

2) COOH, OH,

3) $C(=O)NR_7R_8$ en donde R_7 y R_8 son iguales o diferentes y se seleccionan de H o alquilo inferior,

R_2 es CH_3, y

R_3 es X_2-R'_3 en donde

- X_2 es un solo enlace, alquileno de C_1-C_4 o alquenileno de C_2-C_6 y
- R'_3 es:

fenilo,

heterociclo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

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- X_3 es un solo enlace, y

- R_{17} es:

1) CN, OH, CF_3, =O, alcoxi de C_1-C_6, halógeno,

2) $COOR_5$, SO_2R_5,

3) $C(=O)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, $C(=O)R_5$, $C(=O)NR_5R_6$, R_5 o R_6,

4) heterociclo optativamente sustituido con uno o varios grupos R_5.

12. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es S.

13. Un compuesto definido en cualquiera de las reivindicaciones 1 a 11, en donde Y es O.

14. Un compuesto seleccionado del grupo formado por:
Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,
Ácido (1R*, 2R*)-2-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,
(S)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fenil-etanol,

2-{2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-etanol,

{1-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclopentil}-metanol,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2,5,6-trifluoro-benzoico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-propil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclobutil-amina,

3-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-azepan-2-ona,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclopentil-amina,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-cicloheptil-amina,

(S)-2-[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-3-metil-butan-1-ol,

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2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-metil-propan-1-ol,

terc-Butil-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-isopropil-amina,

Ácido 4-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(1-etil-propil)-amina,

4-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,2-diamina,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-fluoro-fenil)-amina,

N-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexano-1,4-diamina,

(1R*, 2S*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(4-trifluorometil-fenil)-amina,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

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3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

Ácido 5-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

(1-Aza-biciclo[2.2.2]oct-3-il)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenol,

(R)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-butan-1-ol,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(3-fluoro-fenil)-amina,

(3-Cloro-fenil)-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ácido {3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-acético,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzamida,

Biciclo[2.2.1]hept-2-il-[5-(4-cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

(1R*, 2R*)-2-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

5-(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-2-metoxi-fenol,

Ácido 3-(5-ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino)-benzoico,

Ácido 3-[5-(4-cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-4-hidroxi-benzoico,

(5-Ciclohexil-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-(3-metanosulfonil-fenil)-amina,

(1R*,2R*)-2-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ciclohexil-[5-(2,4-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(2-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[3-metil-5-(4-trifluorometil-fenil)-3*H*-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-piridin-4-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[5-(3-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

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Ciclohexil-[5-(3-metoxi-4-nitro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

2,4-Dicloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Ciclohexil-(3-metil-5-tiofen-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[5-(3,5-dicloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-[5-(2-etil-5-metil-2H-pirazol-3-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Cloro-2,6-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-(5-isoxazol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

Ciclohexil-[3-metil-5-(5-piridin-2-il-tiofen-2-il)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

[5-(4-Cloro-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

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2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-6-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

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C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

2-Cloro-5-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dietilamino-etil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-propil)-N-etil-bencenosulfonamida,

Metil éster del ácido [5-(4-Cloro-fenil)-2-ciclohexilimino-[1,3,4]tiadiazol-3-il]-acético,

Metil éster del ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 3-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-hidroxi-etil)-benzamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2-diol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,6-dimetoxi-fenol,

6-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-piridin-2-ol,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencen-1,2,3-triol,

2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinolin-8-ol,

Ciclohexil-(3-metil-5-pirazin-2-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

5-[(E)-2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-vinil]-2-metoxi-fenol,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol,

Ciclohexil-(3-metil-5-quinolin-8-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-dimetil-amina,

4-(5-Ciclohexilimino-4-methyl-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

[5-(5-Cloro-1H-indol-2-il)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina; compuesto con ácido trifluoro-metanesulfónico,

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2-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol; compuesto con ácido 1,1,1-trifluoro-metanosulfónico,

Ciclohexil-[5-(3,4-dimetoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

[5-(3-Bromo-4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

Ciclohexil-[5-(4-metoxi-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-amina,

Ciclohexil-(3-metil-5-fenil-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenol,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-hidroxi-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Sal de clorhidrato de 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-*N*-(2H-tetrazol-5-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

Ciclohexil-{5-[4-(1-etil-1H-tetrazol-5-il)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isobutil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

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4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-N-metil-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-1-(3-hidroximetil-piperidin-1-il)-metanona,

terc-Butil éster del ácido 2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido 2-({1-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-metanoil}-amino)-3-(4-hidroxi-fenil)-propiónico, compuesto con ácido 2,2,2-trifluoro-acético,

terc-Butil éster del ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

Ácido (S)-2-[4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-piridin-2-il-piperazin-1-il)-metanona,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-[4-(4-fluoro-fenil)-piperazin-1-il]-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-pirimidin-2-il-piperazin-1-il)-metanona,

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[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-(4-metil-piperazin-1-il)-metanona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(1-etil-pirrolidin-2-ilmetil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-Bencil-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-1)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

[5-(4-((N-ciano-N'-etilmorfolin)-carboximidamido)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

Ciclohexil-(3-metil-5-piridin-3-il-3H-[1,3,4]tiadiazol-2-iliden)-amina,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

(5-Benzo[1,3]dioxol-5-il-3-metil-3H-[1,3,4]tiadiazol-2-iliden)-ciclohexil-amina,

Ciclohexil-[3-metil-5-(3,4,5-trimetoxi-fenil)-3H-[1,3,4]tiadiazol-2-iliden]-amina,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

Ácido 5-[5-(4-Ciano-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(cis-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[4-Metil-5-(trans-4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

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4-[5-((1R*, 2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

4-[5-((1R*, 3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzonitrilo,

(1R*, 3R*))-3-[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanol,

Ácido 4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-morfolin-4-il-etil)-benzamida,

Ácido 4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoico,

4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

4-[5-((1R*, 3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-N-(2-hidroxi-1,1-dimetil-etil)-benzamida,

N-terc-Butil-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

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N-(1,1-dimetil-3-oxo-butil)-4-[5-(1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

N-(2-Ciano-1,2,2-trimetil-etil)-4-[5-((1R*, 3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Metil éster del ácido 1-{4-[5-((1R*,3R*)-3-hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzoilamino}-ciclopropanocarboxílico,

4-(5-Ciclopentilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-benzamida,

4-(5-Cicloheptilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-[5-(4-Fluoro-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3-Hidroxi-fenilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

Ácido 5-[5-(4-Carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-fluoro-benzoico,

4-[4-Metil-5-(4-metil-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Biciclo[2.2.1]hept-2-ilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2R*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,2S*)-2-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[4-Metil-5-(3-oxo-ciclohexilimino)-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(3,3-Difluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-((1R*,3R*)-3-Fluoro-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

4-[5-(Ciclohex-3-enilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-benzamida,

(1R*,3R*)-3-{3-Metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-ilidenamino}-ciclohexanol,

Ácido 3-[5-(4-cloro-fenyl)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-2-hidroxi-benzoico,

Ácido 3-[5-(4-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

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Ácido 2-fluoro-5-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-ciclohexanocarboxílico,

[5-(4-metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-piperidin-1-il amina,

[5-(4-Metanosulfonil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-(tetrahidro-piran-4-il)-amina,

Ácido 3-[5-(4-acetilamino-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

N-{4-[5-(trans-4-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3S*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{4-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-fenil}-acetamida,

N-{5-[5-((1R*,3R*)-3-Hidroxi-ciclohexilimino)-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il]-piridin-2-il}-acetamida,

3-[5-(4-Cloro-fenil)-3-metil-3H/-[1,3,4]tiadiazol-2-ilidenamino]-benzonitrilo,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-N-hidroxi-benzamidina,

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3-{3-[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-fenil}-[1,2,4]oxadiazol-5-ol,

[5-(4-Bromo-3-metil-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzonitrilo,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metil-benzamida,

[5-(4-Bromo-3-metoxi-fenil)-3-metil-2,3-dihidro-[1,3,4]tiadiazol-2-il]-ciclohexil-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-hidroxi-benzamida,

Metil éster del ácido 4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-nitro-benzoico,

Metil éster del ácido 2-amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

Metil éster del ácido 2-acetilamino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-1H-quinazolin-2,4-diona,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2-metoxi-bencenosulfonamida,

Metil éster del ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(3-ciano-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[3-metil-5-piridin-2-il-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

Ácido 3-[5-(4-Cloro-3-sulfamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzonitrilo,

Ciclohexil-{3-metil-5-[4-(1H-tetrazol-5-il)-fenil]-3H-[1,3,4]tiadiazol-2-iliden}-amina,

Ciclohexil-[3-metil-5-(4-nitro-fenil)-3H-[1,3,4] tiadiazol-2-iliden]-amina,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenilamina,

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[5-(4-(N-ciano-N'-(2-dimetilaminoetil)-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida,

[5-(4-(bis-etilsulfonilamino)-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(1-(2-dimetilaminoetil)amino-2-nitro-vinilamino)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

(E)-N^1-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-2-nitro-eten-1,1-diamina,

[5-(*N*-ciano-*N'*-metil-4-carboximidamido-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[5-(4-(N-ciano-N'-amino-carboximidamido)-fenil)-3-metil-3*H*-[1,3,4]tiadiazol-2-iliden]-ciclohexil-amina,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-amida del ácido etanosulfónico,

[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4] tiadiazol-2-il)-fenil]-urea,

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

Metil éster del ácido 2-cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Cloro-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

Metil éster del ácido 4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzoico y

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]oxadiazol-2-il)-benzamida

15. Un compuesto de acuerdo con la reivindicación 14, seleccionado del grupo formado por:

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2-metoxi-bencen-1,3-diol; compuesto con ácido trifluoro-metanosulfónico,

5-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-2,3-dimetoxi-fenol; compuesto con ácido trifluoro-metanosulfónico,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

{5-[4-Cloro-3-(4-metil-piperazin-1-sulfonil)-fenil]-3-metil-3H-[1,3,4]tiadiazol-2-iliden}-ciclohexil-amina,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-bencenosulfonamida,

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2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-isopropil-N-(2-morfolin-4-il-etil)-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-[2-(2-metoxi-etoxi)-etil]-bencenosulfonamida,

C-Cloro-(ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(dimetilamino-hidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2,3-dihidroxi-propil)-N-etil-bencenosulfonamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-etil-N-(2-hidroxi-3-pirrolidin-1-il-propil)-bencenosulfonamida,

3-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-quinolin-8-il-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2,6-dimetoxi-piridin-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-isopropil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-etil-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-(2-dimetilamino-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N-piridin-4-ilmetil-benzamida,

2-Cloro-5-(5-ciclohexilimino-4-metil-4,5-dihidro[1,3,4]tiadiazol-2-il)-N,N-dietil-bencenosulfonamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-metil-benzamida,

terc-butil éster del ácido 2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico,

ácido (S)-2-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoilamino]-3-(4-hidroxi-fenil)-propiónico; compuesto con ácido 2,2,2-trifluoro-acético,

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4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(3,4,5-trimetoxi-bencil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-[3-(4-metil-piperazin-1-il)-propil]-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-piridin-3-ilmetil-benzamida,

N-(1-Bencil-piperidin-4-il)-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-etil-2H-pirazol-3-il)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-morfolin-4-il-etil)-benzamida,

4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-N-(2-pirrolidin-1-il-etil)-benzamida,

ácido 3-[5-(4-carbamoil-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-ilidenamino]-benzoico,

[5-(4-Cloro-fenil)-3-metil-3H-[1,3,4]tiadiazol-2-iliden]-[3-(1H-tetrazol-5-il)-fenil]-amina,

metil éster del ácido 2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzoico,

2-Amino-4-(5-ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-benzamida,

7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-3H-quinazolin-4-ona,

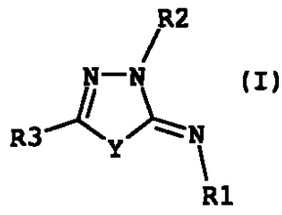
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7-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-quinazolin-4-ilamina,

N-[4-(5-Ciclohexilimino-4-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-acetamida, y

1-[4-(Ciclohexilimino-metil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-fenil]-3-(2-dimetilamino-etil)-urea.

16. Una composición farmacéutica que comprende un compuesto de la fórmula (I)



en donde:

- Y es O o S;

- R_1 es:

alquilo de C_1-C_{10},

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo,

o un grupo policíclico;

cada uno optativamente sustituido con uno o varios grupos X_1-R_4, idénticos o diferentes, en donde:

- X_1 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, cicloalquileno, arileno o heterociclo divalente, y

- R_4 es:

1) H, =O, NO_2, CN, halógeno, haloalquilo inferior, alquilo inferior, bioisóstero de ácido carboxílico,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_7R_8$, $C(=S)NR_7R_8$, $C(=N-CN)NR_7R_8$, $C(=N-SO_2NH_2)NR_7R_8$, $C(=CH-NO_2)NR_7R_8$, $C(=NR_7)NHR_8$, $C(=NR_7)R_8$, $C(=NR_9)NHR_8$, $C(=NR_9)R_8$, $SO_2NR_7R_8$ o NR_7R_8 en donde R_7 y R_8 son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=NR_9)NHR_{10}$, $C(=NR_9)R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$ o $C(=S)NR_9R_{10}$;

- R_2 es:

alquilo inferior,

alquenilo de C_2-C_{10},

alquinilo de C_2-C_{10},

cicloalquilo,

cicloalquenilo,

heterociclo,

arilo;

cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, bioisóstero de ácido carboxílico, haloalquilo inferior,

halógeno,

2) $COOR_5$, OR_5, SO_2R_5,

3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$ o $NR_{11}R_{12}$ en donde R_{11} y R_{12} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R_3 es $X_2-R'_3$ en donde:

- X_2 es un solo enlace o,

un grupo seleccionado de alquileno de C_1-C_4, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

1) H, alquilo de C_1-C_3, cicloalquilo de C_3-C_4, arilo, heterociclo, =O, CN,

2) OR_5, $=NR_5$ o,

3) $NR_{13}R_{14}$ en donde R_{13} y R_{14} son iguales o diferentes y se seleccionan de R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$;

- R'_3 es:

cicloalquilo,

cicloalquenilo,

arilo,

heterociclo,

o un grupo policíclico;

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cada uno optativamente sustituido con uno o varios grupos X_3-R_{17}, idénticos o diferentes, en donde:

- X_3 es:

un solo enlace, alquileno inferior, alquenileno de C_2-C_6, alquinileno de C_2-C_6, cicloalquileno, arileno, heterociclo divalente o un grupo heterocíclico divalente, y

- R_{17} es:

1) H, =O, NO_2, CN, haloalquilo inferior, halógeno, bioisóstero de ácido carboxílico, cicloalquilo,

2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5, SOR_5, SO_3R_5, SR_5, OR_5,

3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$, $C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$ o $NR_{15}R_{16}$ en donde R_{15} y R_{16} son iguales o diferentes y se seleccionan de OH, R_5, R_6, $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5, $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ o $C(=NR_9)R_{10}$,

4) heterociclo optativamente sustituido con uno o varios grupos R_5;

en donde,

- R_5 y R_6 son iguales o diferentes y se seleccionan de:

- H,

- alquilo inferior, alquenilo de C_2-C_6, alquinilo de C_2-C_6;

- X_4-cicloalquilo, X_4-cicloalquenilo, X_4-arilo, X_4-heterociclo o X_4-grupo policíclico, en donde X_4 es un solo enlace, alquileno inferior o alquenilo de C_2-C_6;

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cada uno optativamente sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de:

- halógeno, =O, $COOR_{20}$, CN, OR_{20}, alquilo inferior optativamente sustituido con OR_{20}, O-alquilo inferior optativamente sustituido con OR_{20}, C(=O)-alquilo inferior, haloalquilo inferior, X_5-N(R_{19})-R_{18}

en donde X_5 es un solo enlace o alquileno inferior y R_{18}, R_{19} y R_{20} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- X_6-heterociclo, X_6-arilo, X_6-cicloalquilo, X_6-cicloalquenilo, X_6-grupo policiclico en donde X_6 se selecciona de un solo enlace o alquileno inferior, estos grupos optativamente se sustituyen con uno o varios grupos, idénticos o diferentes, seleccionados de halógenos, $COOR_{21}$, OR_{21}, o $(CH_2)_nNR_{21}R_{22}$ en donde n es 0, 1 o 2 y R_{21} y R_{22} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_9 se selecciona de H, CN, OH, alquilo inferior, O-alquilo inferior, arilo, heterociclo, SO_2NH_2 o X_5-N(R_{19})-R_{18} en donde X_5 es un

solo enlace o alquileno inferior y R_{18} y R_{19} son iguales o diferentes y se seleccionan de H o alquilo inferior;

- R_{10} se selecciona de hidrógeno, alquilo inferior, ciclopropilo o heterociclo;

o un derivado farmacéuticamente aceptable de él,

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junto con un portador farmacéuticamente aceptable,
con la condición de que el compuesto de la fórmula (I) no sea etil éster del ácido 4-[2-Formilimino-5-(4-metoxi-fenil)-[1,3,4] tiadiazol-3-il]-butírico, o
etil éster del ácido 4-[5-(4-cloro-fenil)-2-formilimino-[1,3,4]tiadiazol-3-il]-butírico.

17. Una composición farmacéutica de acuerdo con la reivindicación 16, que comprende un compuesto de la fórmula (I), en donde R_1, R_2, R_3 e Y son lo definico en la reivindicación 18, con la condición de que cuando R_1 es C(=O)-H, R_2 no represente $(CH_2)_3$-C(=O)OCH_2CH_3.

18. Una composición farmacéutica que comprende un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, junto con un portador farmacéuticamente aceptable.

19. Una composición farmacéutica de acuerdo con la reivindicación 16, 17 o 18, para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante.

20. Un método para el tratamiento de una enfermedad para la cual el tratamiento con un inhibidor de PDE7 es relevante, que

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comprende administrar a un mamífero, particularmente a un humano, que lo necesita, una cantidad eficaz de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15.

21. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se debe tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

22. Un método de acuerdo con la reivindicación 20, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

24. El uso de un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 15, para la fabricación de un medicamento para el tratamiento de enfermedades para las cuales el tratamiento con un inhibidor de PDE7 es relevante.

24. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, enfermedades inflamatorias, enfermedades respiratorias, enfermedades del CNS, enfermedades alérgicas, enfermedades endócrinas o exócrinas del páncreas, o enfermedades gastrointestinales.

25. El uso de acuerdo con la reivindicación 23, en donde la enfermedad que se ha de tratar se selecciona de dolor visceral, enfermedad inflamatoria del intestino, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirida (SIDA), o rechazo de trasplantes.

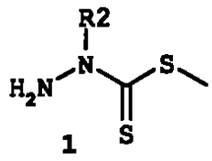
26. Un compuesto de la fórmula (I), definido en cualquiera de las reivindicaciones 1 a 15, como medicamento.

27. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reividindicación 1, con disulfuro de

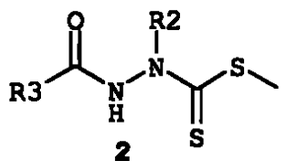
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carbono y MeX donde X es un grupo saliente para obtener un compuesto de la fórmula 1



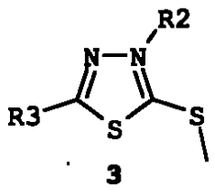
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(b) reacción del S-metilditiocarbazato 1 con un cloruro de acilo R_3COCl en donde R_3 es lo definido en la reivindicación 1 para obtener un metilditiocarbazato acilado 2



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(c) ciclación del metilditiocarbazato acilado 2 en un 1,3,4-tiadiazol 3



3

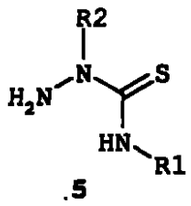
(d) reacción del 1,3,4-tiadiazol 3 con una amina R_1NH_2 en donde R_1 es lo definido en reivindicación 1, para obtener el compuesto de la fórmula (I) en donde Y es S,

(e) aislación del compuesto de la fórmula (I).

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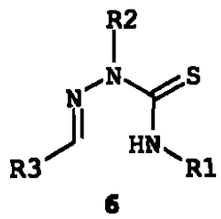
28. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de una hidrazina sustituida R_2NHNH_2 en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$ en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5



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(b) reacción de la tiosemicarbazida 5 con un aldehído R_3CHO en donde R_3 es lo definido en la reivindicación 1, para obtener la tiosemicarbazona 6



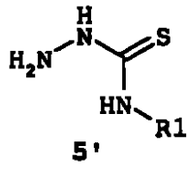
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(c) ciclación de la tiosemicarbazona 6 en el compuesto de la fórmula (I) en donde Y es S,

(d) aislación del compuesto de la fórmula (I).

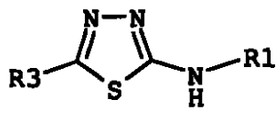
29. El proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 15, en donde Y es S, que comprende los siguientes pasos:

(a) reacción de un ácido carboxílico R_3COOH en donde R_3 es lo definido en reivindicación 1, con la siguiente tiosemicarbazida 5'



5'

para obtener el 1,3,4-tiadiazol 7



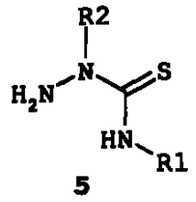
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(b) reacción del 1,3,4-tiadiazol 7 con R_2X, en donde R_2 es lo definido en la reivindicación 1 y X es un grupo saliente para obtener el compuesto de la fórmula (I) en donde Y es S

(c) aislación del compuesto de la fórmula (I).

30. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 12, 14 o 14, que comprende los siguientes pasos:

(a) reacción de un ácido carboxílico R_3COOH, en donde R_3 es lo definido en la reivindicación 1, con la siguiente tiosemicarbazida 5



5

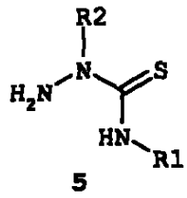
para obtener el compuesto final de la fórmula I en donde Y es S,

(b) aislación del compuesto de la fórmula (I).

31. Un proceso para la preparación de un 1,3,4-tiadiazol de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 1 a 11 o 13, en donde Y es S, que comprende los siguientes pasos:

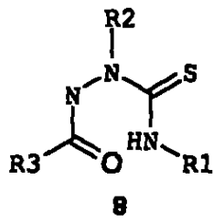
(a) reacción de una hidrazina sustituida R_2NHNH_2, en donde R_2 es lo definido en la reivindicación 1, con un isotiocianato sustituido $SCNR_1$, en donde R_1 es lo definido en la reivindicación 1, para obtener la tiosemicarbazida sustituida 5,

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(b) reacción de la tiosemicarbazida 5 con R_3-C(=O)Cl, en donde R_3 es lo definido en la reivindicación 1, para formar la tiosemicarbazida 8 deseada



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(d) ciclación de la tiosemicarbazida 8 en el compuesto final de la fórmula I en donde Y es O,

(d) aislación del compuesto de la fórmula (I).