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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00058843 00000001 Folios: 121
Fecha (AMD): 2000-10-31 16:58:00
Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

E. S D.

Re: P1.- JANSSEN PHARMACEUTICA N.V.- Solicitud de Patente de
Invención para "INHIBIDORES IL-5 NO ESTEROIDALES,
PROCEDIMIENTOS E INTERMEDIARIOS PARA SU PREPARACIÓN
Y COMPOSICIONES FARMACEUTICAS QUE COMPRENDEN
DICHOS INHIBIDORES".- Clase A61 .-Expediente número 00-
058.843 .-

1. Me refiero a mi solicitud de patente arriba nombrada de fecha 4 de Agosto de 2000.

2. Anexos me permito presentar a usted:

(1) Copias autenticas (2) de las primeras solicitudes de patente presentadas para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber:

(a) Copia autentica debidamente certificada de la solicitud europea número 99870170.0 de 6 de Agosto de 1999, junto con la traducción oficial No. LLC-073-2000, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(b) Copia autentica debidamente certificada de la solicitud europea número 99126035.7 de 27 de Diciembre de 1999, junto con la traducción oficial No. LLC-074-2000, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial del señor Gabriel Rueda Chadid quien elaboró la traducción de las solicitudes europeas número 99870170.0 y 99126035.7, respecto de las cuales se reivindica prioridad en el presente caso.

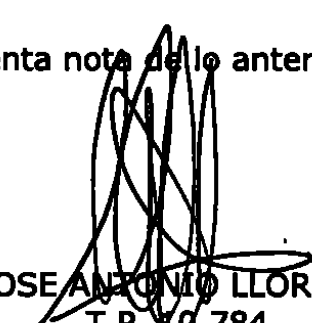
(3) Documentos de traspaso (3) en los cuales:

15608

- (a) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de Janssen Cilag S.A., de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 425811 de 30 de Agosto de 2000; y
- (b) Traducción Oficial No. 139/00, debidamente legalizada hasta por el Ministerio 525965 de 4 de Septiembre de 2000, correspondiente a las partes pertinentes de dicho documento de traspaso.
- (c) Se acredita el traspaso que la sociedad Janssen Cilag S.A. hace a favor de JANSSEN PHARMACEUTICA NV., de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 425812 de 30 de Agosto de 2000;
- (d) Traducción Oficial No. 140/00, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 525966 de 4 de Septiembre de 2000, correspondiente a las partes pertinentes de dicho documento de traspaso;
- (e) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de JANSSEN PHARMACEUTICA NV., de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 425810 de 30 de Agosto de 2000;
- (f) Traducción Oficial No. 141/00, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 525967 de 4 de Septiembre de 2000, correspondiente a las partes pertinentes de dicho documento de traspaso;

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,


JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DE MINISTERIO DE
RELACIONES EXTERIORES

HACE CONSTAR

Que el señor Gabriel Rueda, se encuentra debidamente
registrado ante este Ministerio, como traductor e
interprete oficial para los idiomas INGLES -ESPAÑOL,
ESPAÑOL - INGLES.

Para efectos de esta certificacion el interesado presento
copia autenticada de la certificacion del Ministerio de
Justicia acerca de la vigencia de la resolucion
1982

Dada en Santafe de Bogotá, D C , a los diez y nueve dias -
(19) del mes de diciembre de 1994

Neibón Sánchez Torres
Jefe Area de Legalizaciones

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA, 03 SET 1998
PABLO MENDEZ BARRERA

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA, 23 NOV 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

1987

República de Colombia



Ministerio de Justicia y del Derecho

EL SECRETARIO GENERAL DEL MINISTERIO DE
JUSTICIA Y DEL DERECHO

CERTIFICA

Que por Resolución 5996 del 29 de noviembre de 1982, le fue expedida licencia para ejercer funciones de Traductor e Interprete Oficial en los idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES a GABRIEL RUEDA CHADID, identificado con la cedula de ciudadanía No 17 124 145 expedida en Bogota Que dicha resolución se encuentra vigente en la fecha

A solicitud del interesado, en Santafe de Bogota D C, a los 17 días del mes de noviembre de 1994

JORGE LOIS SARDAL SARDAL

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
01 SET 2000
PAULO MENDEZ BARAJAS

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
17 AGO 1998

COMO NOTARIO SEXTO DE
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HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
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SANTAFE DE BOGOTA
03 NOV 1998

COMO NOTARIO SEXTO DE
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QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
01 JUL 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
03 SET 1998
PAULO MENDEZ BARAJAS

EAR/cccc

TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFE DE BOGOTA
SECRETARIA GENERAL

LA SUSCRITA SECRETARIA DEL H. TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL
DE SANTAFE DE BOGOTA,

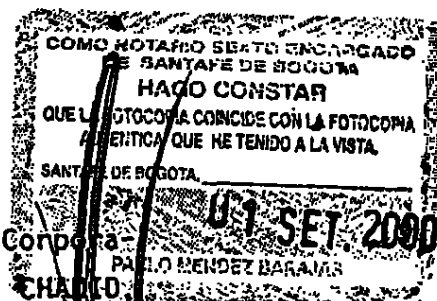
C E R T I F I C A :

Que el Acuerdo No. 183 de diciembre 3 de 1982 emanado de esta Corporación, por medio del cual dió posesión al señor GABRIEL RUEDA CHADID, identificado con Cédula de Ciudadanía número 17.124.145 de Bogotá, como TRADUCTOR E INTERPRETE OFICIAL de los idiomas INGLES-ESPAÑOL-ESPAÑOL-INGLES, en virtud de la Resolución No. 5996, se encuentra VIGENTE.

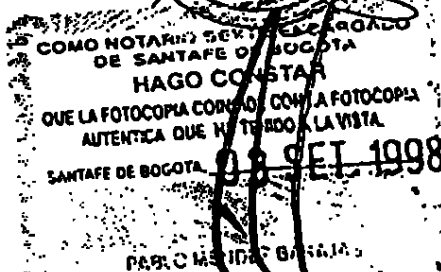
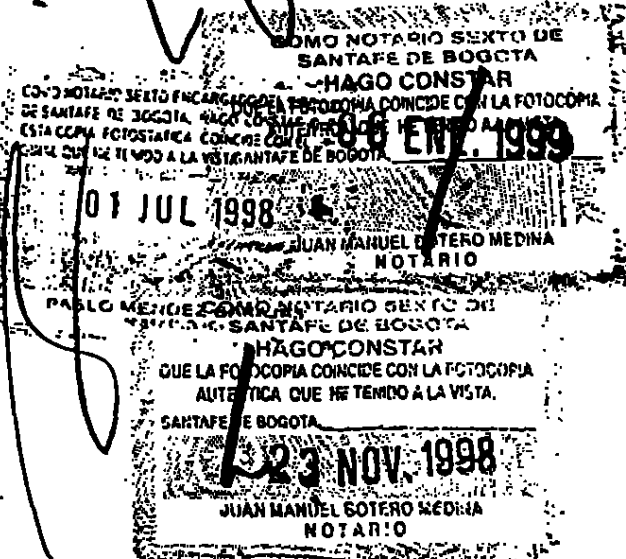
Se expide en Santafé de Bogotá D.C., a dieciseis (16) de noviembre de mil novecientos noventa y cuatro (1994).

MARIA INES RODRIGUEZ TORRES
SECRETARIA

CTM./



21 AGO. 1998



~~10912~~

Janssen Pharmaceutica N.V. C-JAB1520-COL

REF: LLC-073-2000. La presente es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial).

OFICINA EUROPEA DE PATENTES.

CERTIFICADO

Los documentos adjuntos son fiel copia de la solicitud de patente Europea según la descripción que aparece en la siguiente página, presentada originalmente.

No. de Solicitud de la Patente 99870170.0

El Presidente de la Oficina Europea de Patentes

I.L.C. HATTEN-HECKMAN

(Firmado)

LA HAYA, 23 / 08 / 00

Ju
GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

OFICINA EUROPEA DE PATENTES

Solicitud No.: 99870170.0
Fecha de Presentación: 06 / 08 / 99

Solicitante:
JANSSEN PHARMACEUTICA N.V.
2340 Beerse
BELGIUM

Título del Invento:
Derivados del interlequin-5 inhibidor 6-azauracil

Clasificación Internacional de la Patente:
C07D417/10, C07D417/14, C07D413/10, A61K31/53

Estados Contratantes Designados en la Fecha de la
Presentación:

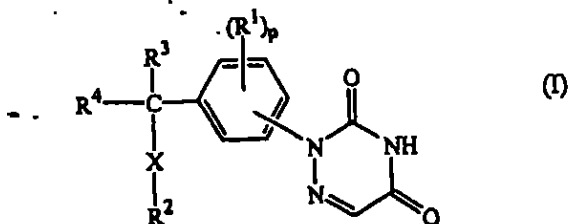
AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE

[Signature]
GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

REIVINDICACIONES

06-08-1999 EP99870170.0

1. Un compuesto que tiene la siguiente formula:



un N-óxido, una sal de adición farmacéuticamente aceptable o una de sus formas esterequímicamente isoméricas, donde:

p representa un entero que es 0, 1, 2, 3 o 4;

X representa O, S, NR⁵ o un enlace directo o -X-R² tomados conjuntamente pueden representar ciano;

Y representa O, S, NR⁵, o S(O)₂;

cada R¹ independientemente representa C(=O)-Z-R¹⁴, alquilo C₁₋₈, halo, polihaloC₁₋₈alquilo, hidroxilo, mercapto, alquilo C₁₋₈, alquiltio C₁₋₈, alquilcarbonilo C₁₋₈, arilo, ciano, nitro, Het³, R⁶, NR⁷R⁸ o alquilo C₁₋₄ sustituido por C(=O)-Z-R¹⁴, Het³, R⁶ o NR⁷R⁸;

R² representa Het¹, cicloalquilo C₃₋₇ sustituido opcional por C(=O)-Z-R¹⁴, alquilo C₁₋₈ o alquilo C₁₋₈ sustituido por uno o dos sustitutos que se seleccionan a partir de C(=O)-Z-R¹⁴, hidroxilo, ciano, amino, mono- o di(alquilo C₁₋₄)amino, alquilo C₁₋₈ sustituido opcionalmente por C(=O)-Z-R¹⁴, alquilsulfonilo C₁₋₈, cicloalquilo C₃₋₇ sustituido opcionalmente por C(=O)-Z-R¹⁴, arilo, arilo, arilo, arilo, Het¹, Het¹oxi y Het¹tio; y si X es O, S, o NR⁵, entonces R² puede también representar el aminotiocarbonilo, alquilcarbonilo C₁₋₄ sustituido opcionalmente por C(=O)-Z-R¹⁴, alquiltiocarbonilo

C₁₋₄ sustituido opcionalmente por C(=O)-Z-R¹⁴, arilcarbonilo, ariltiocarbonilo, Het¹carbonilo o Het¹tiocarbonilo;

R³ representa hidrógeno, alquilo C₁₋₈ o cicloalquilo C₃₋₇;

R⁴ representa hidrógeno, alquilo C₁₋₈ o cicloalquilo C₃₋₇; o

R³ y R⁴ tomados conjuntamente forman un alcanediilo C₂₋₈;

R⁵ representa hidrógeno o alquilo C₁₋₄;

cada R⁶ independientemente representa el alquilsulfonilo C₁₋₈, aminosulfonilo, mono- o di(alquilo C₁₋₄)-aminosulfonilo, mono- o di(benzil)aminosulfonilo, polihaloC₁₋₈alquilsulfonilo, alquilsulfinilo C₁₋₈, fenilC₁₋₄alquilsulfonilo, piperazinilsulfonilo, aminopiperidinilsulfonilo, piperidinilaminosulfonilo, N-alquilo C₁₋₄-N-piperidinilaminosulfonilo o mono-o di(alquilo C₁₋₄)aminoC₁₋₄alquilsulfonilo;

cada R⁷ y cada R⁸ se seleccionan independientemente a partir del hidrógeno, alquilo C₁₋₄, hidroxilC₁₋₄alquilo, dihidroxilC₁₋₄alquilo, arilo, arilC₁₋₄alquilo, alquiloC₁₋₄alquilo, alquilcarbonilo C₁₋₄, arilcarbonilo, Het³carbonilo, mono- o di(alquilo C₁₋₄)aminoC₁₋₄alquilo, arilaminocarbonilo, arilaminotiocarbonilo, Het³aminocarbonilo, Het³aminotiocarbonilo, cicloalquilo C₃₋₇, piridinilC₁₋₄alquilo, alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, Het³, Het⁴ y R⁶;

R⁹ y R¹⁰ se seleccionan cada uno independientemente del hidrógeno, alquilo C₁₋₄, hidroxilC₁₋₄alquilo, dihidroxilC₁₋₄alquilo, fenilo, fenilC₁₋₄alquilo, alquiloC₁₋₄alquilo, alquilcarbonilo C₁₋₄, fenilcarbonilo, Het³carbonilo, mono- o di(alquilo C₁₋₄)aminoC₁₋₄alquilo, fenilaminocarbonilo,

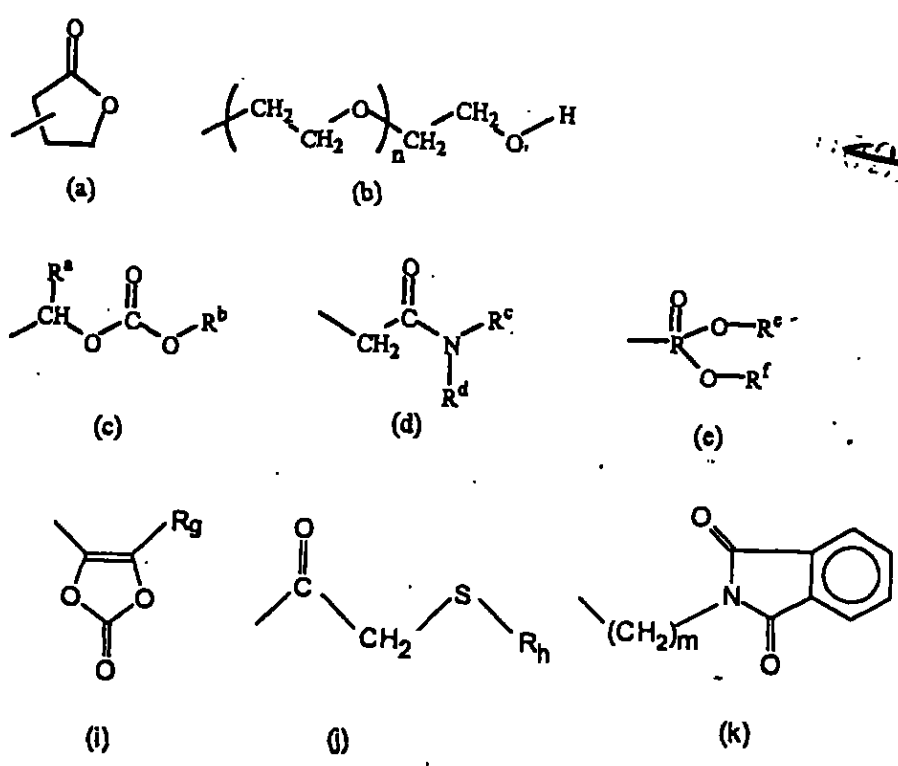
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fenilaminotiocarbonilo, Het³aminocarbonilo,
Het³aminotiocarbonilo, cicloalquilo C₃₋₇, piridinilC₁₋₄alquilo, alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, Het³, Het⁴ y R⁶;

cada R¹¹ independientemente se selecciona del hidroxilo, mercapto, ciano, nitro, halo, trihalometilo, alquilo C₁₋₄ sustituido opcionalmente por C(=O)-Z-R¹⁴, formilo, trihaloC₁₋₄alquilsulfonilo, R⁶, NR⁷R⁸, C(=O)NR¹⁵R¹⁶, -C(=O)-Z-R¹⁴, -Y-alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, arilo arilo, arilcarbonilo, cicloalquilo C₃₋₇ sustituido opcionalmente por C(=O)-Z-R¹⁴, cicloalquilo C₃₋₇ sustituido opcionalmente por C(=O)-Z-R¹⁴, ftalimido-2-ilo, Het³ y C(=O)Het³;

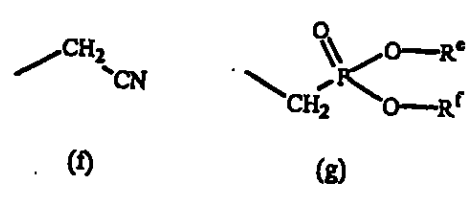
R¹² y R¹³ son cada uno seleccionados independientemente a partir del hidrógeno, alquilo C₁₋₄, hidroxiloC₁₋₄alquilo, dihidroxiloC₁₋₄alquilo, fenilo, fenilC₁₋₄alquilo, alquiloC₁₋₄alquilo C₁₋₄, alquilcarbonilo C₁₋₄, fenilcarbonilo, mono- o di(alquilo C₁₋₄)aminoalquilo C₁₋₄, fenilaminocarbonilo, fenilaminotiocarbonilo, cicloalquilo C₃₋₇, piridinilC₁₋₄alquilo, alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-alcanediilo C₁₋₄-C(=O)-Z-R¹⁴ y R⁶;

cada R¹⁴ representa independientemente el alquilo C₁₋₄ sustituido por uno o más sustitutos que se seleccionan a partir del fenilo, di- alquilamino C₁₋₄, ciano, Het¹ y cicloalquilo C₃₋₇, hidrógeno, acilo C₁₋₂₀ (que tiene una cadena recta o bifurcada, saturada o insaturada de hidrocarbón que tiene de 1 a 20 átomos de carbono), alquilo C₁₋₂₀, cicloalquilo C₃₋₇, polihaloC₁₋₂₀alquilo o un radical de la siguiente fórmula



donde n es 0 a 5 y m es 1 a 4;
 R^a, R^b, R^c, R^d, R^e y R^f son cada una independientemente hidrógeno, alquilo C₁₋₈ o cicloalquilo C₃₋₇; o
 R^e y R^f tomados conjuntamente pueden formar -CH₂-CH₂-, -CH₂-CH₂-CH₂-, o -CH₂-CH₂-CH₂-CH₂-;
 R^h y R^h son cada uno independientemente alquilo C₁₋₄;

cada Z independientemente representa O, S, NH, -CH₂-O- o -CH₂-S- donde -CH₂- se adhiere al grupo carbonilo;
 -Z-R¹⁴ tomada conjuntamente forma un radical de la siguiente formula



R¹⁵ y R¹⁶ son cada uno y de manera independiente seleccionados a partir del dihidroxí alquiloC₁₋₄, arilo, arilo alquiloC₁₋₄, alquiloC₁₋₄alquiloC₁₋₄, -C(=O)-Z-R¹⁴, arilcarbonilo, mono- o di(alquiloC₁₋₄)amino alquiloC₁₋₄,

arilaminocarbonilo, arilaminotiocarbonilo,
 Het³aminocarbonilo, Het³aminotiocarbonilo, piridinil
 alquiloC₁₋₄, Het³, Het⁴ o R⁶;

aminocarbonilmetileno o mono-o di(alquilo C₁₋₄)aminocarbonilmetileno;

arilo representa el fenilo sustituido opcionalmente por uno, dos o tres sustitutos cada uno de ellos seleccionados independientemente a partir del nitro, azido, ciano, halo, hidroxil, alquilo C₁₋₄, cicloalquilo C₃₋₇, alquilo C₁₋₄, formilo, polihalo alquiloC₁₋₄, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-Z-R¹⁴, R⁶, -O-R⁶, fenilo, Het³, C(=O)Het³ y alquiloC₁₋₄ sustituido por uno o más sustitutos donde cada uno de ellos se selecciona independientemente a partir del halo, hidroxil, alquilo C₁₋₄, C(=O)-Z-R¹⁴, -Y-alcanediloC₁₋₄-C(=O)-Z-R¹⁴, Het³ o NR⁹R¹⁰;

Het¹ representa un heterociclo seleccionado a partir del pirrolilo, pirrolinilo, imidazolilo, imidazolinilo, pirazolilo, pirazolinilo, triazolilo, tetrazolilo, furanilo, tetrahydrofuranilo, tienilo, tiolanilo, dioxolanilo, oxazolilo, oxazolinilo, isoxazolilo, tiazolilo, tiazolinilo, isotiazolilo, tiadiazolilo, oxadiazolilo, piridinilo, pirimidinilo, pirazinilo, piranilo, piridazinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, dioxanilo, ditianilo, tritiano, triazinilo, benzotienilo, isobenzotienilo, benzofuranilo, isobenzofuranilo, benzotiazolilo, benzoxazolilo, indolilo, isoindolilo, indolinilo, purinilo, 1H-pirazolo[3,4-d] pirimidinilo, benzimidazolilo, quinolilo, isoquinolilo, cinnolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, tiazolopiridinilo, oxazolopiridinilo e imidazo[2,1-b]-

tiazolilo; donde los mencionados heterociclos cada uno de ellos y en forma independiente pueden sustituirse opcionalmente por uno, dentro de lo posible, dos o tres sustitutos cada uno seleccionados independientemente del Het², R¹¹ y alquilo C₁₋₄ sustituido opcionalmente por uno o dos sustitutos seleccionados independientemente del Het² y R¹¹:

Het² representa un heterociclo seleccionado del pirrolilo, pirrolinilo, imidazolilo, imidazolinilo, pirazolilo, pirazolinilo, triazolilo, tetrazolilo, furanilo, tetrahidrofuranilo, tienilo, tiolanilo, dioxolanilo, oxazolilo, oxazolinilo, isoxazolilo, tiazolilo, tiazolinilo, isotiazolilo, tiadiazolilo, oxadiazolilo, piridinilo, pirimidinilo, pirazinilo, piranilo, piridazinilo, dioxanilo, ditianilo, tritianilo, triazinilo, benzotienilo, isobenzotienilo, benzofuranilo, isobenzofuranilo, benzotiazolilo, benzoxazolilo, indolilo, isoindolilo, indolinilo, purinilo, 1H-pirazolo[3,4-d] pirimidinilo, benzimidazolilo, quinolilo, isoquinolilo, cinnolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, tiazolopiridinilo, oxazolopiridinilo e imidazo[2,1-b]-tiazolilo; donde los mencionados heterociclos cada uno de ellos y en forma independiente pueden sustituirse opcionalmente por uno, dentro de lo posible, dos o tres sustitutos cada uno seleccionados independientemente del Het⁴, R¹¹ y alquilo C₁₋₄ sustituido opcionalmente por uno o dos sustitutos seleccionados independientemente del Het⁴ y R¹¹;

Het³ representa un heterociclo monocíclico seleccionado del pirrolidinilo, piperidinilo, piperazinilo, morfolinilo,

tiomorfolinilo y tetrahidropiranilo; donde los heterociclos monocíclicos mencionados cada uno de ellos independientemente pueden ser opcionalmente sustituidos por uno, dos, tres o cuatro posibles sustitutos, cada uno de ellos seleccionados independientemente del hidroxilo, alquilo C₁₋₄, alquilo C₁₋₄, alquilo C₁₋₄, alquilo C₁₋₄, piperidinilo, NR¹²R¹³, C(=O)-Z-R¹⁴, R⁸ y alquilo C₁₋₄ sustituido por uno o dos sustitutos seleccionados independientemente del hidroxilo, alquilo C₁₋₄, fenilo, C(=O)-Z-R¹⁴, -Y-alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, R⁸ y NR¹²R¹³;

Het⁴ representa un heterociclo monocíclico seleccionado del pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, furanilo, tienilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, tiadiazolilo, oxadiazolilo, piridinilo, pirimidinilo, pirazinilo, pirazinilo, piranilo, piridazinilo y triazinilo a condición de que

- R² sea distinto del alquilo C₁₋₄-alquilo C₁₋₄, aminocarbonilo; y
- R⁷, R⁸, R⁹ y R¹⁰ sean distintos del aminocarbonilo, alquilo C₁₋₄-alquilo C₁₋₄, hidroxilo alquilo C₁₋₄, alquilo C₁₋₄, alquilo C₁₋₄, C(=O)-O-R¹⁴, alcanediilo C₁₋₄-C(=O)-O-R¹⁴ e -Y-alcanediilo C₁₋₄-C(=O)-O-R¹⁴; y
- R¹² y R¹³ sean distintos del alquilo C₁₋₄-alquilo C₁₋₄, hidroxilo alquilo C₁₋₄, alquilo C₁₋₄; y
- R¹¹ es distinto de C(=O)-O-R¹⁴, Y-alcanediilo C₁₋₄ - C(=O)-OR¹⁴, C(=O)NH₂, C(=O)NHalquilo C₁₋₄ o C(=O)NHcicloalquilo C₃₋₇; y
- R¹⁴ es distinto del hidrógeno, alquilo C₁₋₄,

- cicloalquiloC₃₋₇, aminocarbonilmetileno, mono- o di(alquiloC₁₋₄)aminocarbonilmetileno en el evento de que Z sea O; y
- R¹⁵ y R¹⁶ son distintos del aminocarbonilo, alquilcarboniloxiC₁₋₄-alquilcarboniloC₁₋₄, hidroxialquilcarboniloC₁₋₄ o alquiloxicarbonilcarboniloC₁₋₄; y
 - Arilo es distinto del fenilo sustituido por C(=O)-O-R¹⁴ C(=O)NH₂, C(=O)NHalquiloC₁₋₄, C(=O)NHcicloalquiloC₃₋₇ y/o por alquiloC₁₋₄ sustituido por C(=O)-O-R¹⁴ o Y-alcanediiloC₁₋₄ - C(=O)-O-R¹⁴; y
 - Het³ es distinto del heterociclo monocíclico sustituido por C(=O)-O-R¹⁴ y/o por alquiloC₁₋₄ sustituido por C(=O)-O-R¹⁴ y/o Y-alcanediiloC₁₋₄ - (=O)-O-R¹⁴; y
 - El compuesto mencionado de la formula (I) contiene por lo menos un medio -C(=O)-Z-R¹⁴.

2. Un compuesto según se describe en la reivindicación 1 donde la porción 6-azauracilo se encuentra en una posición relativa al átomo de carbono que lleva los sustitutos -X-R², R³ y R⁴.

3. Un compuesto según se describió en las reivindicaciones 1 o 2 donde R² es un heterociclo monocíclico seleccionado a partir de pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, furanilo, tienilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, tiadiazolilo, oxadiazolilo, piridinilo, pirimidinilo, pirazinilo, piranilo, piridazinilo y triazinilo, donde los mencionados heterociclos monocíclicos pueden cada uno independientemente y en forma opcional sustituirse por uno, o si es posible dos o tres sustitutos cada uno de ellos seleccionados independientemente

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del Het². R¹¹ y alquilo C₁₋₄ sustituido opcionalmente por Het² o R¹¹.

4. Un compuesto según se describió en una de las reivindicaciones 1 a 3 donde R³ y R⁴ son ambos metilo y -X-R² es Het¹.

5. Un compuesto según se describió en una de las reivindicaciones 1 a 4 donde p es 1 o 2 y cada R¹ es cloro.

6. Un compuesto que comprende un portador farmacéuticamente aceptable y como ingrediente activo una cantidad terapéuticamente eficaz de un compuesto según se reivindica en una de las reivindicaciones 1 a 5.

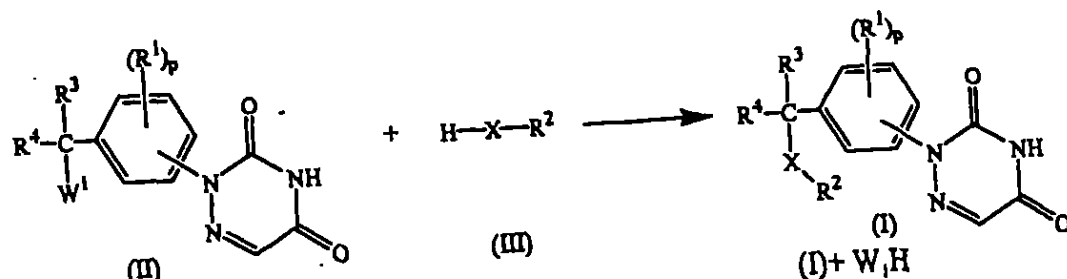
7. Un proceso para la preparación de un compuesto según se reivindica en la reivindicación 6, donde un portador farmacéuticamente aceptable se mezcla íntimamente con una cantidad terapéuticamente eficaz de un compuesto según se define en una de las reivindicaciones 1 a 5.

8. Un compuesto según se define en una de las reivindicaciones 1 a 5 para utilizarse como medicamento.

9. La utilización de un compuesto según se define en una de las reivindicaciones 1 a 5 para la elaboración de un medicamento para el tratamiento de enfermedades inflamatorias eosinófilo-dependientes.

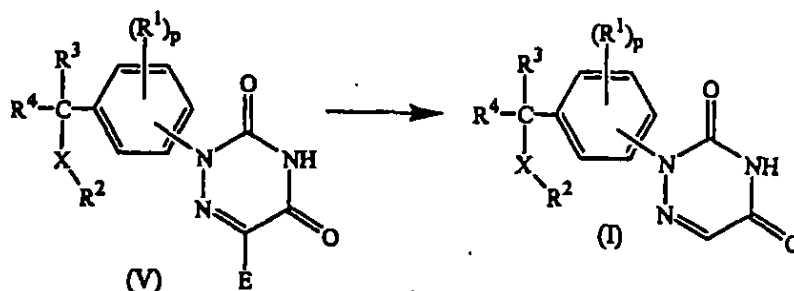
10. Un proceso para la preparación de un compuesto según se define en la reivindicación 1, caracterizado por,

(a) la reacción de un intermedio de la formula (II) donde W^1 es un grupo adecuado saliente que tiene un reactivo apropiado de la formula (III) opcionalmente en un solvente inerte a la reacción y opcionalmente en presencia de una base a una temperatura entre -70°C y la temperatura de reflujo;



donde R^1 , R^2 , R^3 , R^4 , p y X corresponden a la definición dada en la reivindicación 1 o;

b) eliminación del grupo E de una triazinediona de la formula (V)



donde E es un electrón apropiado que atrae al grupo y R^1 , R^2 , R^4 , X y p corresponden a la definición dada en la reivindicación 1; y

si se desea se transforman los compuestos de la formula (I) en cada una de las siguientes transformaciones conocidas en la técnica y posteriormente si se desea se transforman los

compuestos de la formula (I), en una sal de adición ácida no tóxica terapéuticamente activa por tratamiento con un ácido, o en una sal de adición base no tóxica terapéuticamente activa por tratamiento con una base, o inversamente, la transformación de la forma de la sal de adición ácida en la base libre por medio del tratamiento con alcali, o la transformación de la sal de adición de base en el ácido libre por tratamiento con ácido; y además si se desea, la preparación de las formas estereoquímicamente isoméricas de sus formas N-óxido.

11. Un proceso de marcación de un receptor que comprende los siguientes pasos:

- a) radioetiquetado de un compuesto según se define en la reivindicación 1;
- b) administración de dicho compuesto radioetiquetado al material biológico,
- c) detección de las emisiones provenientes del compuesto radioetiquetado.

12. Un proceso de imagen de un órgano, caracterizado por. la administración de una cantidad suficiente de un compuesto radioetiquetado de la formula (I) en una composición apropiada, y la detección de las emisiones provenientes del compuesto radioactivo.

La anterior es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción fue realizada por GABRIEL RUEDA CHADID (Traductor Oficial). Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firmo.

Santafé de Bogotá D.C., Septiembre 4 del 2000.

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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99870170.0

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 23/08/00
LA HAYE, LE



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**Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Pag 2 de l'attestation**

Anmeldung Nr.:
Application no.: 99870170.0
Demanda n°:

Anmeldetag:
Date of filing: 06/08/99
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
JANSSEN PHARMACEUTICA N.V.
2340 Beerse
BELGIUM

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Interleukin-5 inhibiting 6-azauracil derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat:
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International Patent classification:
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C07D417/10, C07D417/14, C07D413/10, A61K31/53

Am Anmeldetag benannte Vertragsstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/OK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:

**NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM**

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- 5 The present invention concerns IL-5 inhibiting 6-azauracil derivatives useful for treating eosinophil-dependent inflammatory diseases; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

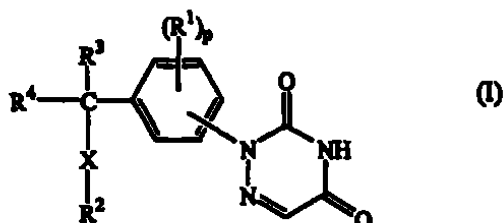
10 Eosinophil influx, leading to subsequent tissue damage, is an important pathogenic event in bronchial asthma and allergic diseases. The cytokine interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces the differentiation of eosinophils in bone marrow and, primes eosinophils for activation in peripheral blood and sustains their survival in tissues. As such, IL-5 plays a critical role in the process of eosinophilic inflammation. Hence, the possibility that inhibitors of IL-5 production would reduce the
15 production, activation and/or survival of eosinophils provides a therapeutic approach to the treatment of bronchial asthma and allergic diseases such as, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent inflammatory diseases.

- 20 Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as the only drugs with remarkable efficacy for bronchial asthma and atopic dermatitis, but they cause various serious adverse reactions such as diabetes, hypertension and cataracts. Therefore, it would be desirable to find non-steroidal compounds having the ability to inhibit IL-5 production in human T-cells and which have little or no adverse
25 reactions.

US 4,631,278 discloses α -aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-benzeneacetonitriles and US 4,767,760 discloses 2-(substituted phenyl)-1,2,4-triazine-3,5(2H,4H)-diones, all having anti-protozoal activity, in particular, anti-coccidial
30 activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones as anticoccidial agents. WO99/02505 discloses 6-azauracil derivatives which prove to be potent inhibitors of the production of IL-5.

-2-

The present invention is concerned with the compounds of formula



the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

5 p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR^5 or a direct bond or $-X-R^2$ taken together may represent cyano;

Y represents O, S, NR^5 , or $S(O)_2$;

each R^1 independently represents $C(=O)-Z-R^{14}$, C_{1-6} alkyl, halo, polyhalo C_{1-6} alkyl,

hydroxy, mercapto, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylcarbonyloxy, aryl, cyano,

10 nitro, Het^3 , R^6 , NR^7R^8 or C_{1-4} alkyl substituted with $C(=O)-Z-R^{14}$, Het^3 , R^6 or NR^7R^8 ;

R^2 represents Het^1 , C_{3-7} cycloalkyl optionally substituted with $C(=O)-Z-R^{14}$, C_{1-6} alkyl or C_{1-6} alkyl substituted with one or two substituents selected from $C(=O)-Z-R^{14}$,

hydroxy, cyano, amino, mono- or di(C_{1-4} alkyl)amino, C_{1-6} alkyloxy optionally

substituted with $C(=O)-Z-R^{14}$, C_{1-6} alkylsulfonyloxy, C_{3-7} cycloalkyl optionally

15 substituted with $C(=O)-Z-R^{14}$, aryl, aryloxy, arylthio, Het^1 , Het^1 oxy and Het^1 thio; and if

X is O, S or NR^5 , then R^2 may also represent aminothiocarbonyl, C_{1-4} alkylcarbonyl

optionally substituted with $C(=O)-Z-R^{14}$, C_{1-4} alkylthiocarbonyl optionally substituted

with $C(=O)-Z-R^{14}$, arylcarbonyl, arylthiocarbonyl, Het^1 carbonyl or Het^1 thiocarbonyl;

R^3 represents hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl;

20 R^4 represents hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl; or

R^3 and R^4 taken together form a C_{2-6} alkanediyl;

R^5 represents hydrogen or C_{1-4} alkyl;

each R^6 independently represents C_{1-6} alkylsulfonyl, aminosulfonyl, mono- or di-

(C_{1-4} alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl,

25 polyhalo C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, phenyl C_{1-4} alkylsulfonyl,

piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*- C_{1-4} alkyl-*N*-

piperidinylaminosulfonyl or mono- or di(C_{1-4} alkyl)amino C_{1-4} alkylsulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkyl-carbonyl, arylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl,

- 5 Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³ and R^6 ;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl,

- 10 phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³ and R^6 ;

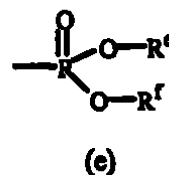
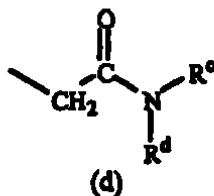
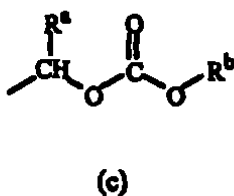
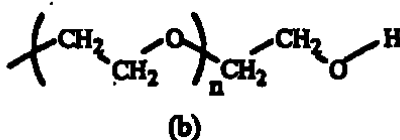
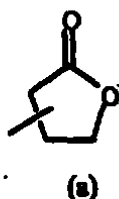
each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4} alkyloxy optionally substituted with C(=O)-Z- R^{14} , formyl,

- 15 trihalo C_{1-4} alkylsulfonyloxy, R^6 , NR^7R^8 , C(=O) $NR^{15}R^{16}$, -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , aryl, aryloxy, arylcarbonyl, C_{3-7} cycloalkyl optionally substituted with C(=O)-Z- R^{14} , C_{3-7} cycloalkyloxy optionally substituted with C(=O)-Z- R^{14} , phthalimide-2-yl, Het³, Het⁴ and C(=O)Het³;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} and R^6 ;

- 25 each R^{14} independently represents C_{1-4} alkyl substituted with one or more substituents selected from phenyl, di- C_{1-4} alkylamino, cyano, Het¹ and C_{3-7} cycloalkyl, hydrogen, C_{1-20} acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C_{1-20} alkyl, C_{3-7} cycloalkyl, polyhalo C_{1-20} alkyl or a radical of formula

-4-

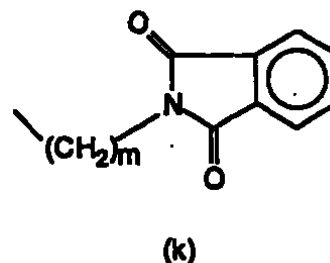
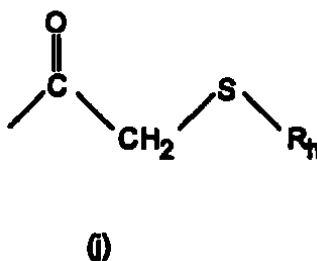
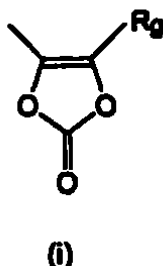
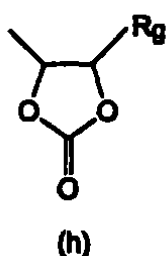


wherein n is 0 to 5;

R^a, R^b, R^c, R^d, R^e and R^f are each independently hydrogen, C₁₋₄alkyl or C₁₋₇cycloalkyl; or

5

R^e and R^f taken together may form -CH₂-CH₂-, -CH₂-CH₂-CH₂- or -CH₂-CH₂-CH₂-CH₂-; or a radical of formula



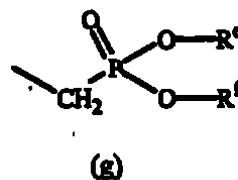
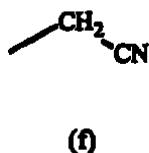
wherein m is 1 to 4

10

R₁ and R₂ are each independently C₁₋₄ alkyl;

each Z independently represents O, S, NH, -CH₂-O- or -CH₂-S- whereby -CH₂- is attached to the carbonyl group;

-Z-R¹⁴ taken together form a radical of formula



15

R¹⁵ and R¹⁶ are each independently selected from dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, -C(=O)-Z-R¹⁴, arylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, pyridinylC₁₋₄alkyl, Het³ or R⁶;

aminocarbonylmethylene or mono-or di(C₁₋₄alkyl)aminocarbonylmethylene;

aryl represents phenyl optionally substituted with one, two or three substituents each

independently selected from nitro, azido, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-Z-R¹⁴,

5 R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³ or NR⁹R¹⁰;

Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazoliny,

pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl,

10 thiolanyl, dioxolanyl, oxazolyl, oxazoliny, isoxazolyl, thiazolyl, thiazolinyl,

isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl,

pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl,

dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl,

15 isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indoliny, purinyl,

1H-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnoliny,

phtalazinyl, quinazoliny, quinoxaliny, thiazolopyridiny, oxazolopyridiny and

imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each

independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or

20 two substituents independently selected from Het² and R¹¹;

Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazoliny,

pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl,

thiolanyl, dioxolanyl, oxazolyl, oxazoliny, isoxazolyl, thiazolyl, thiazolinyl,

isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl,

25 pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl,

benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl,

indoliny, purinyl, 1H-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl,

isoquinolyl, cinnoliny, phtalazinyl, quinazoliny, quinoxaliny, thiazolopyridiny,

oxazolopyridiny and imidazo[2,1-b]thiazolyl; wherein said heterocycles each

30 independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R¹¹ and C₁₋₄alkyl optionally substituted

with one or two substituents independently selected from R¹¹;

Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹²R¹³, C(=O)-Z-R¹⁴, R⁶ and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, phenyl, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, R⁶ and NR¹²R¹³;

Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl provided however that

- R² is other than C₁₋₄alkyloxycarbonylC₁₋₄alkyl, aminocarbonyl; and
- R⁷, R⁸, R⁹ and R¹⁰ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl C(=O)-O-R¹⁴, C₁₋₄alkanediylC(=O)-O-R¹⁴ and -Y-C₁₋₄alkanediylC(=O)-O-R¹⁴; and
- R¹² and R¹³ are other than C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl, C₁₋₄alkylcarbonylcarbonyl; and
- R¹¹ is other than C(=O)-O-R¹⁴, Y-C₁₋₄alkanediyl - C(=O)-OR¹⁴, C(=O)NH₂, C(=O)NHC₁₋₄alkyl or C(=O)NHC₃₋₇cycloalkyl; and
- R¹⁴ is other than hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl, aminocarbonylmethylene, mono- or di (C₁₋₄alkyl) aminocarbonylmethylene in the event Z is 0; and
- R¹⁵ and R¹⁶ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl or C₁₋₄alkyloxycarbonylcarbonyl; and
- Aryl is other than phenyl substituted with C(=O)-O-R¹⁴, C(=O)NH₂, C(=O)NHC₁₋₄alkyl, C(=O)NHC₃₋₇cycloalkyl and/or with C₁₋₄alkyl substituted with C(=O)-O-R¹⁴ or Y-C₁₋₄alkanediyl - C(=O)-O-R¹⁴; and
- Het³ is other than a monocyclic heterocycle substituted with C(=O)-O-R¹⁴ and/or with C₁₋₄alkyl substituted with C(=O)-O-R¹⁴ and/or Y-C₁₋₄alkanediyl - C(=O)-O-R¹⁴; and
- The said compound of formula (I) contains at least one - C(=O)-Z-R¹⁴ moiety.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₃₋₇cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl,

- cyclohexyl and cycloheptyl; C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C₁₋₆alkyl is meant to include C₁₋₄alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like C₁₋₂₀alkyl is meant to include C₁₋₆alkyl and the higher homologues thereof having 7 to 20 carbon atoms such as, for example, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl, nonadecyl, eicosyl and the like C₁₋₂₀alkyl is meant to include C₁₋₂₀alkyl except for C₁₋₄alkyl; polyhaloC₁₋₄alkyl is defined as polyhalosubstituted C₁₋₄alkyl, in particular C₁₋₄alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhaloC₁₋₆alkyl is defined as polyhalosubstituted C₁₋₆alkyl; polyhaloC₁₋₂₀alkyl is defined as polyhalosubstituted C₁₋₂₀alkyl. The term C₁₋₄alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C₂₋₆alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 2 to 6 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like.
- Het¹, Het², Het³ and Het⁴ are meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het¹, Het², Het³ and Het⁴, for instance, pyrrolyl also includes 2*H*-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranyl includes 2*H*-pyranyl and 4*H*-pyranyl.

- The heterocycles represented by Het¹, Het², Het³ and Het⁴ may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it

-8-

is benzthiazolyl, it may be 2-benzthiazolyl, 4-benzthiazolyl, 5-benzthiazolyl, 6-benzthiazolyl and 7-benzthiazolyl.

The C₁₋₂₀acyl is derived from

5	acetic acid	CH ₃ COOH	tridecanoic acid	C ₁₃ H ₂₅ COOH
	propionic acid	C ₂ H ₅ COOH	myristic acid	C ₁₄ H ₂₇ COOH
	butyric acid	C ₃ H ₇ COOH	pentadecanoic acid	C ₁₅ H ₂₉ COOH
	valeric acid	C ₄ H ₉ COOH	palmitic acid	C ₁₆ H ₃₁ COOH
	hexanoic acid	C ₅ H ₁₁ COOH	heptadecanoic acid	C ₁₇ H ₃₃ COOH
10	heptanoic acid	C ₆ H ₁₃ COOH	stearic acid	C ₁₇ H ₃₅ COOH
	octanoic acid	C ₇ H ₁₅ COOH	oleic acid	C ₁₇ H ₃₃ COOH
	nonanoic acid	C ₈ H ₁₇ COOH	linolic acid	C ₁₇ H ₃₁ COOH
	decanoic acid	C ₉ H ₁₉ COOH	linolenic acid	C ₁₇ H ₂₉ COOH
	undecanoic acid	C ₁₀ H ₂₁ COOH	nonadecanoic acid	C ₁₉ H ₃₇ COOH
15	lauric acid	C ₁₁ H ₂₃ COOH	icosanoic acid	C ₁₉ H ₃₉ COOH

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to
30 comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxy-
35 acetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzene-sulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by
40 treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for
45 example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium,

sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

10 The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide. For example, one or more nitrogen atoms of any of the heterocycles in the definition of Het¹, Het² and Het³ may be *N*-oxidized.

15 Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

20

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

25

30 The compounds of formula (I) and some of the intermediates in the present invention contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

5

An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents; preferably in the para position.

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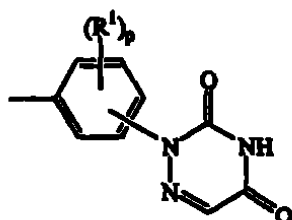
Another interesting group contains those compounds of formula (I) wherein one or more of the following restrictions apply :

- p is 0, 1 or 2;
- X is S, NR^5 , or a direct bond; more in particular NH or a direct bond;
- 15 • each R^1 independently is halo, polyhalo C_{1-6} alkyl, C_{1-6} alkyl, C_{1-6} alkyloxy or aryl, preferably, chloro or trifluoromethyl, more preferably chloro;
- R^2 is Het¹ or C_{1-6} alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4} alkyl)amino, $C(=O)-Z-R^{14}$ C_{1-6} alkyloxy optionally substituted with $C(=O)-Z-R^{14}$, C_{1-6} alkylsulfonyloxy, C_{3-7} cycloalkyl
- 20 optionally substituted with $C(=O)-Z-R^{14}$, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR^5 , then R^2 may also represent aminothiocarbonyl, C_{1-4} alkylcarbonyl optionally substituted with $C(=O)-Z-R^{14}$, C_{1-4} alkylthiocarbonyl optionally substituted with $C(=O)-Z-R^{14}$, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; particularly R^2 is Het¹ or in the event X is NH, R^2
- 25 may also be aminothiocarbonyl or Het¹carbonyl;
- R^3 is hydrogen, methyl, ethyl, propyl or cyclohexyl; preferably, methyl;
- R^4 is hydrogen or methyl; preferably, methyl;
- R^3 and R^4 are taken together to form a 1,4-butanediyl;
- R^6 is C_{1-6} alkylsulfonyl or aminosulfonyl;
- 30 • R^7 and R^8 are each independently hydrogen, C_{1-4} alkyl, Het³ or R^6 ;
- R^9 and R^{10} are each independently hydrogen, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, aminocarbonyl, Het³carbonyl, Het³ or R^6 ;

- R¹¹ is cyano, nitro halo, C₁₋₄alkyloxy, formyl, NR⁹R⁴, C(=O)NR¹⁵R¹⁶, -C(=O)-Z-R¹⁴, aryl, arylcarbonyl, Het³, Het⁴ and C(=O)Het³;
- R¹⁴ is dihydrofuranyl, C₅₋₂₀alkyl, C₁₋₄alkyl substituted with one or more substituents selected from phenyl, C₁₋₄alkylamino, cyano, Het¹ and C₃₋₇cycloalkyl;
- 5 • aryl is phenyl optionally substituted with one, two or three substituents each independently selected from nitro, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-O-R¹⁴, -O-R⁶, phenyl, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, Het³ or NR⁹R¹⁰;
- 10 • Het¹ is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹;
- 15 preferably Het¹ is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹;
- 20 • Het² is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl or benzothienyl, wherein said aromatic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R¹¹ and C₁₋₄alkyl;
- 25 • Het³ is piperidinyl, piperazinyl, morpholinyl and tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkylcarbonyl, piperidinyl and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy and phenyl;
- 30 • Het⁴ is thienyl.

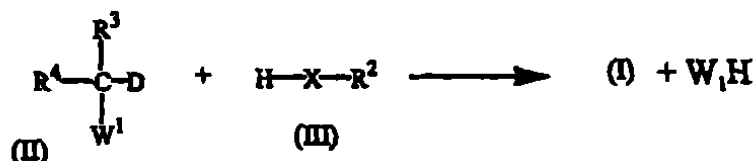
Special compounds are those compounds of formula (I) wherein p is 2 and both R¹ substituents are chloro; more preferably the two chloro substituents are in the ortho positions relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

- 5 Particular compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.
- 10 Other particular compounds are those compounds of formula (I) wherein X is a direct bond and R² is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl,
- 15 wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹; more in particular R² is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.
- 20 Preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are both methyl and -X-R² is Het¹ wherein Het¹ suitably is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.
- More preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are
- 25 both methyl, -X-R² is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.
- 30 In order to simplify the structural representation of the compounds of formula (I), the group



will hereinafter be represented by the symbol D.

Compounds of formula (I) can generally be prepared by reacting an intermediate of
 5 formula (II) wherein W¹ is a suitable leaving group such as, for example, a halogen atom, with an appropriate reagent of formula (III).



Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture
 10 thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no additional reaction-inert solvent is required. The reaction is optionally carried out in the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium bicarbonate, sodiummethanolate and the like. Convenient reaction temperatures range between -70°C and reflux temperature.

15

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

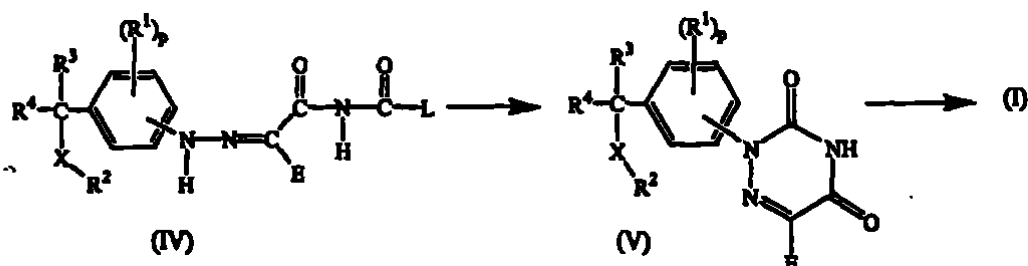
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Some of the compounds and intermediates of the present invention can be prepared according to or analogous to the procedures described in EP-A-0,170,316, EP-A-0,232,932 and WO99/02505.

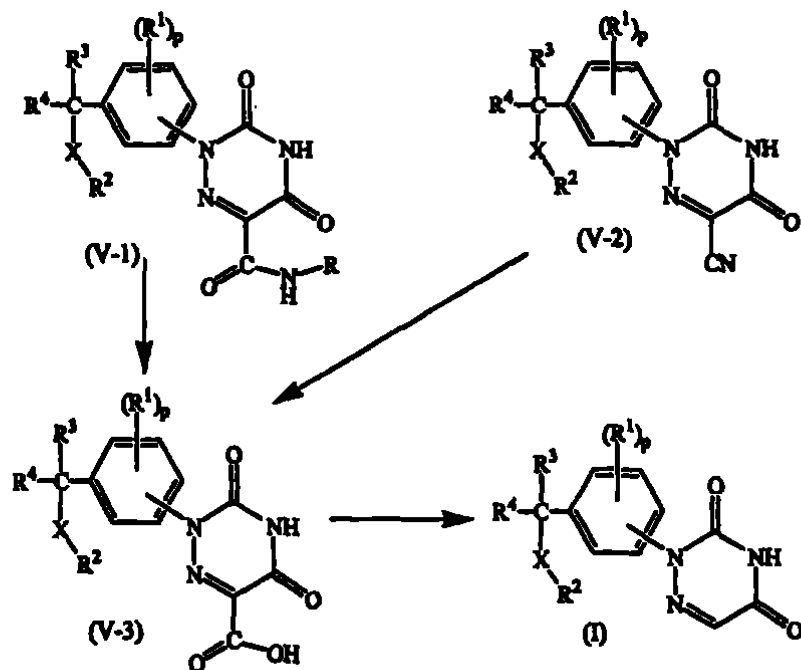
25 Alternatively, for instance, compounds of formula (I) may generally be prepared by cyclizing an

intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C₁₋₆alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide, a cyanide, C₁₋₆alkylsulfonyloxy and the like groups; and eliminating the group E of the thus obtained triazinedione of formula (V).

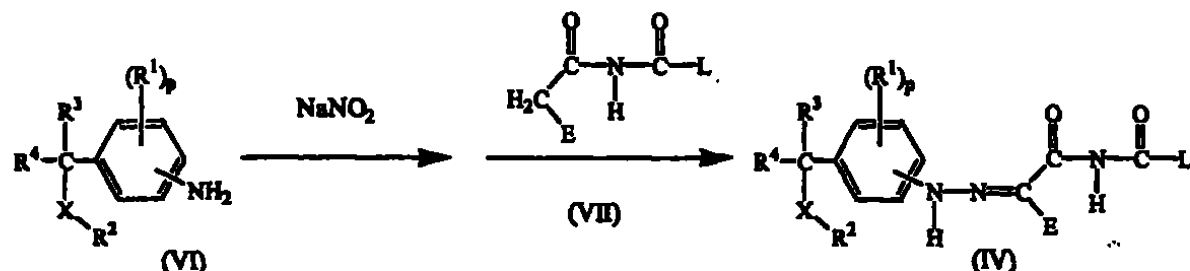
- 5 The cyclization can suitably be carried out by refluxing the intermediate (IV) in acidic medium such as acetic acid and in the presence of a base such as, for example, potassium acetate.



- Depending on its nature, E can be eliminated using various art-known elimination procedures. For example when E is an amide or a cyano moiety, it can be hydrolyzed to a carboxylic moiety by for instance refluxing the intermediate bearing the E group in hydrochloric acid and acetic acid. The thus obtained intermediate can then be further reacted with mercaptoacetic acid or a functional derivative thereof to obtain a compound of formula (I). Said reaction is conveniently carried out at elevated temperatures ranging up to reflux temperature.



A suitable way to prepare intermediates of formula (IV) involves the reaction of an intermediate of formula (VI) with sodium nitrate or a functional derivative thereof in an acidic medium such as for example hydrochloric acid in acetic acid, and preferably in the same reaction mixture, further reacting the thus obtained intermediate with a reagent of formula (VII) wherein L and E are as defined above, in the presence of a base such as, for example, sodium acetate.

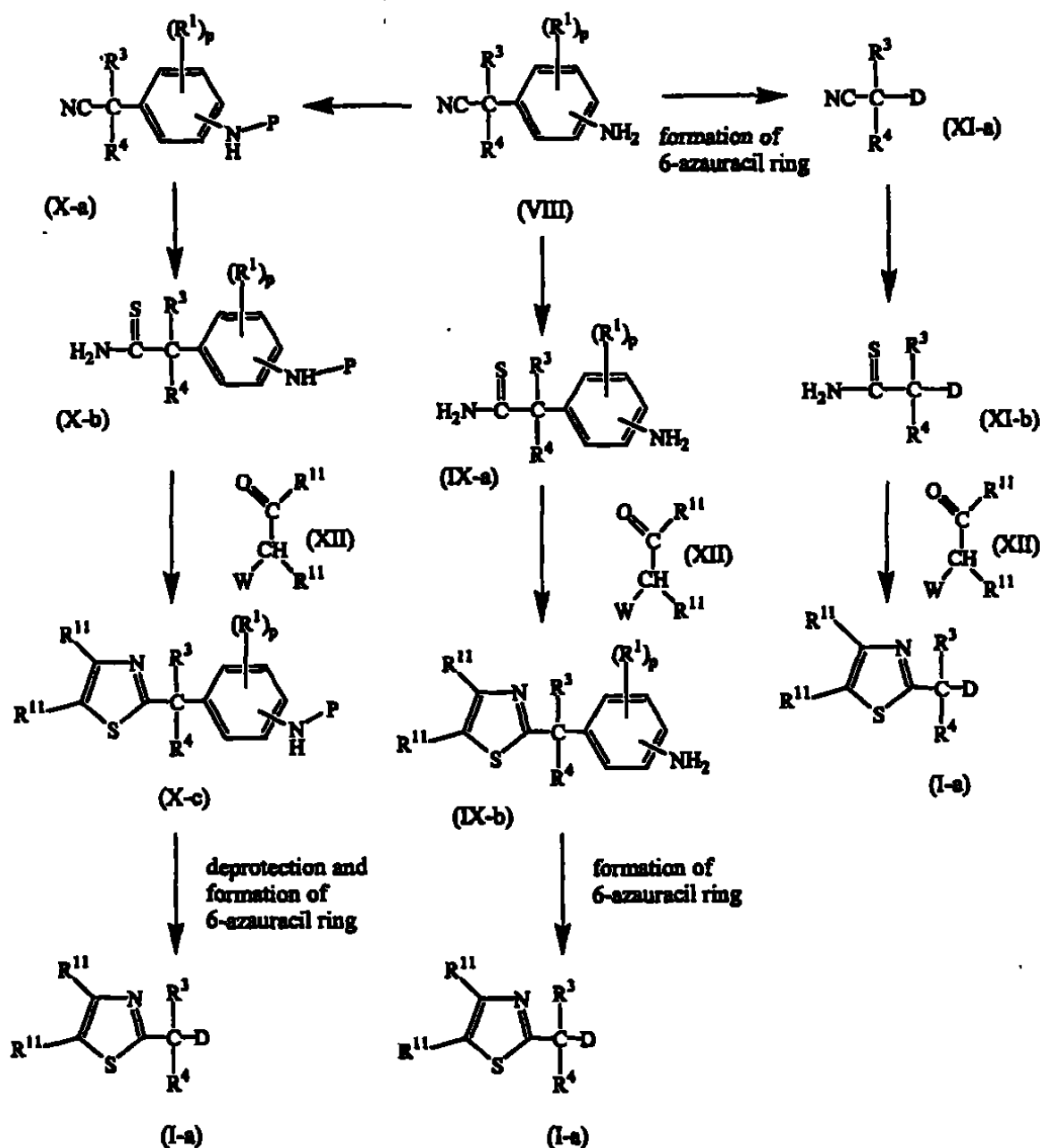


An interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R^2 is an optionally substituted 2-thiazolyl moiety, said compounds being represented by formula (I-a). The optionally substituted 2-thiazolyl moiety can be incorporated in the compounds of formula (I-a) at different stages of the preparation process.

For instance, scheme 1 depicts three possible ways to prepare compounds of formula (I-a).

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Scheme 1



A first pathway involves the reaction of the cyano moiety in an intermediate of formula (VIII) to the corresponding thioamide using H_2S gas in a suitable solvent such as, for example, pyridine and in the presence of a base such as, for example, triethylamine, thus obtaining an intermediate of formula (IX-a). This thioamide can then be cyclized with an intermediate of formula (XII) wherein W is a suitable leaving group such as, for example, a halogen, e.g. bromo, in a suitable solvent such as, for example, ethanol. The amino moiety in the resulting 2-thiazolyl derivative of formula (IX-b) can then be further reacted as described hereinabove to form a 6-azauracil ring, thus obtaining a compound of formula (I-a).

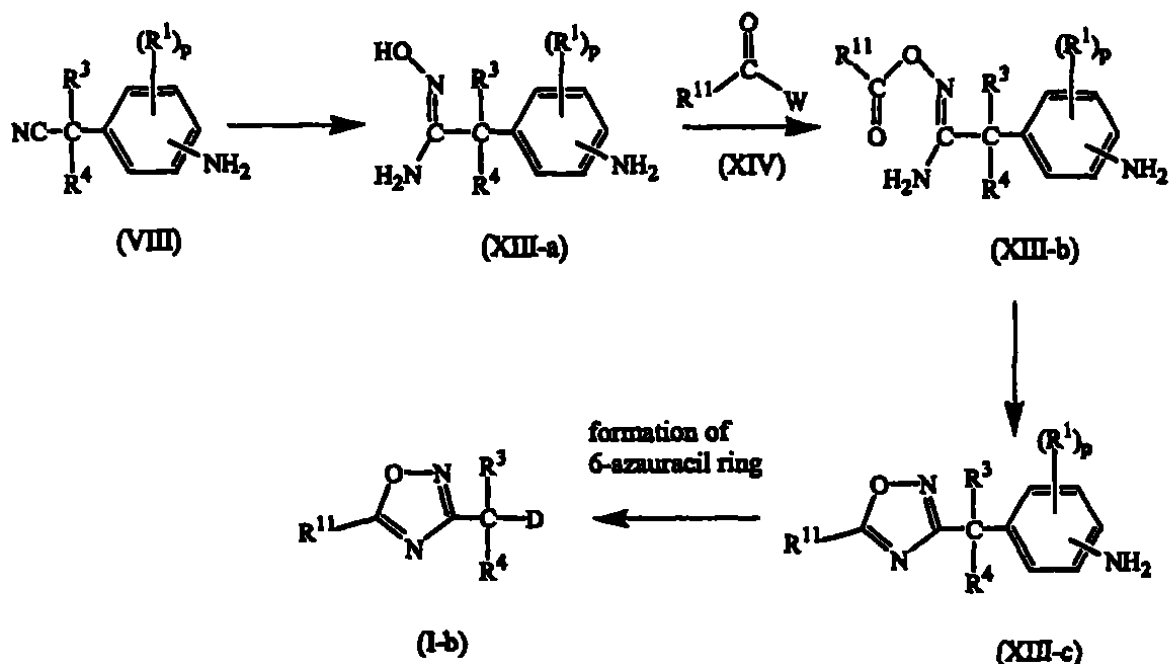
A second pathway to form compounds of formula (I-a) involves first the protecting of the amino moiety in an intermediate of formula (VIII) by introducing a suitable protective group P such as, for example, an alkylcarbonyl group, using art-known protection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (VII) can be reacted with the corresponding anhydride of formula alkyl-C(=O)-O-C(=O)-alkyl in an appropriate solvent such as, for example, toluene. The thus obtained intermediate of formula (X-a) can then be further reacted according to the first pathway described hereinabove. The final step, before formation of the 6-azauracil ring can be initiated after having deprotected the amino moiety using art-known deprotection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (X-c) may be deprotected by reacting them in a suitable solvent such as, for example, ethanol, in the presence of an acid such as, for example, hydrochloric acid.

A third pathway involves first the formation of the 6-azauracil ring as described hereinabove but starting from an intermediate of formula (VIII), and subsequently reacting the thus formed intermediate of formula (XI-a) with H₂S and further reacting the thioamide of formula (XI-b) with an intermediate of formula (XII) as described in the first pathway, to finally form a compound of formula (I-a).

Another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R² is an optionally substituted 1,2,4-oxadiazol-3-yl moiety, said compounds being represented by formula (I-b-1). The optionally substituted 1,2,4-oxadiazol-3-yl moiety can be incorporated at the same stages of the reaction procedure as depicted for the 2-thiazolyl derivatives in scheme 1.

For instance, analogous to one of the three pathways shown in scheme 1, compounds of formula (I-b) can be performed by reacting an intermediate of formula (VIII) as depicted in scheme 2.

Scheme 2

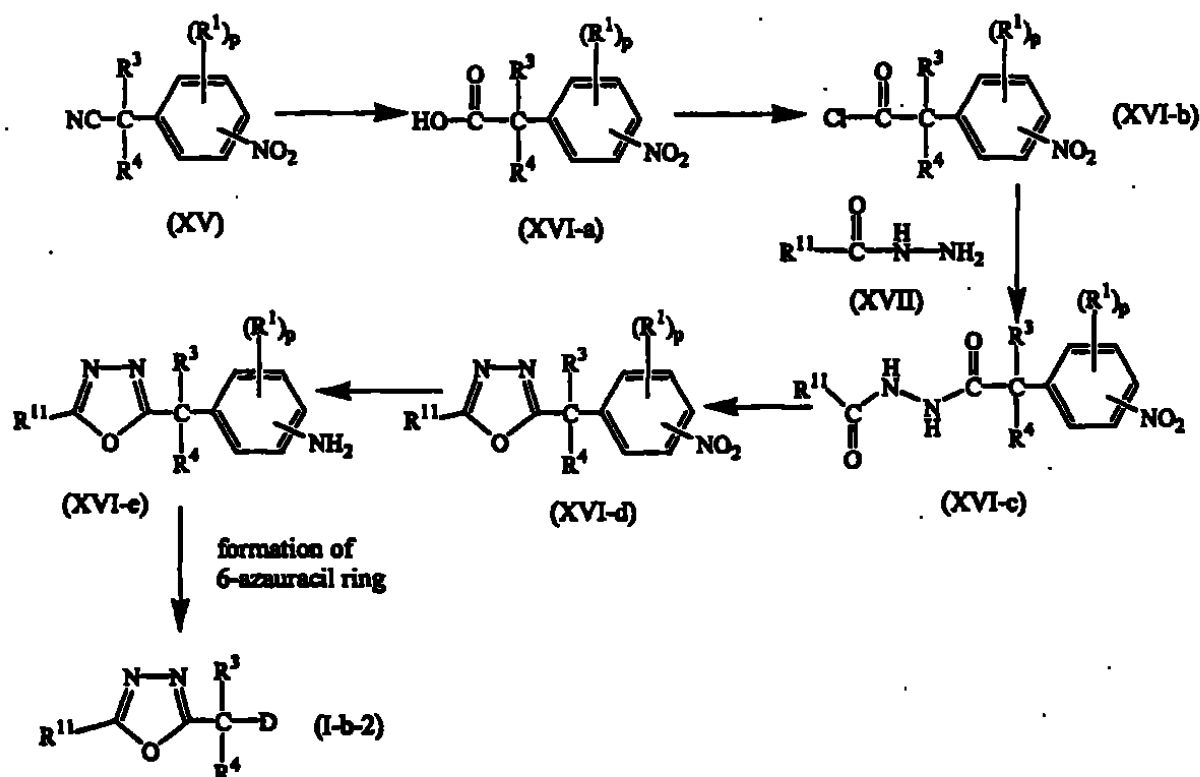


In said scheme 2, the cyano group of an intermediate of formula (VIII) is reacted with hydroxylamine or a functional derivative thereof in a suitable solvent such as, for example, methanol, and in the presence of a base such as, for example sodium methanolate. The thus formed intermediate of formula (XIII-a) is then reacted with an intermediate of formula (XIV) wherein W is a suitable leaving group such as, for example, a halogen, e.g. chloro, in an appropriate solvent such as, for example, dichloromethane, and in the presence of a base, such as, for example, *N,N*-(1-methyl-ethyl)ethanamine. The resulting intermediate of formula (XIII-b) is then cyclized to a 3-oxadiazolyl derivative of formula (XIII-c). The amino moiety in the intermediates of formula (XIII-c) can then be transformed to the 6-azauracil ring as described above.

Still another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R² is an optionally substituted 1,3,4-oxadiazol-2-yl moiety, said compounds being represented by formula (I-b-2).

For instance, compounds of formula (I-b-2) can be prepared as depicted in scheme 3.

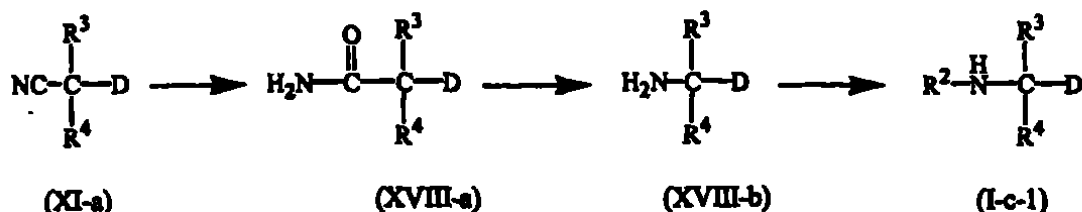
Scheme 3



The nitrile moiety in an intermediate of formula (XV) is transformed into a carboxylic acid moiety using art-known techniques. For instance, the nitrile derivative may be refluxed in a mixture of sulfuric acid and acetic acid in water. The carboxylic acid derivative of formula (XVI-a) may the further be reacted with a chlorinating agent such as, for example, thionyl chloride, to form an acylchloride derivative of formula (XVI-b). Subsequently, The acyl chloride may be reacted with a hydrazine derivative of formula (XVII) in a suitable solvent such as, for example, dichloromethane, and in the presence of a base such as, for example *N,N*-(1-methylethyl)ethaneamine. The thus formed intermediate of formula (XVI-c) may be cyclized to a 1,2,4-oxadiazol-2-yl derivative of formula (XVI-d) in the presence of phosphoryl chloride. As a final step before the formation of the 6-azauracil ring as described above, the nitro group in the intermediates of formula (XVI-e) is reduced to an amino group using art-known reduction techniques such as, for instance, reducing the nitro group with hydrogen in methanol and in the presnece of a catalyst such as Raney Nickel.

Yet another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R² is -NH-R², said compounds being represented by formula (I-c-1). Scheme 4 depicts a suitable pathway to obtain compounds of formula (I-c-1).

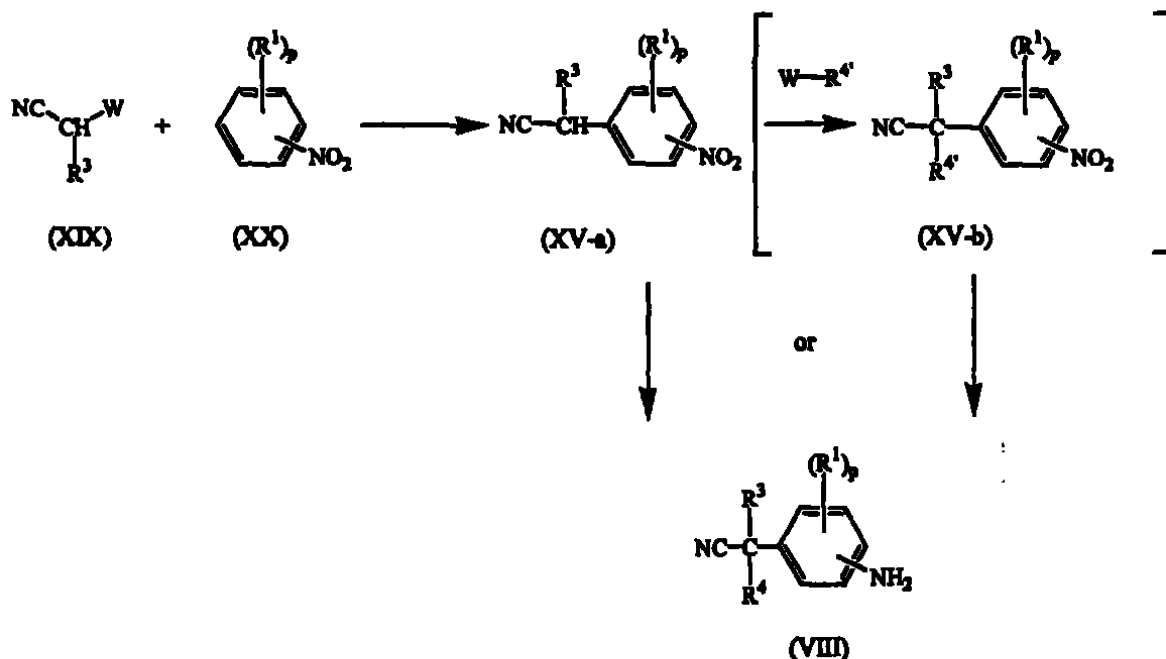
Scheme 4



In said scheme 4, the cyano moiety of an intermediate of formula (XI-a) is hydrolyzed to the corresponding amide using art-known techniques such as, for instance, hydrolysis in the presence of acetic acid and sulfuric acid. The thus formed amide in the intermediates of formula (XVIII-a) can be transformed in an amine using (diacetoxyiodo)benzene or a functional derivative thereof in a suitable solvent such as, for example a mixture of water and acetonitrile. The amine derivative of formula (XVIII-b) can then be reacted with benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate as described in Tetrahedron Letters No.14 (1975) 1219-1222 to obtain a compound, or with a functional derivative thereof such as, for instance, an isothiocyanate, in an appropriate solvent such as, for example, tetrahydrofuran.

Intermediates of formula (VIII) can be prepared as depicted in scheme 5.

Scheme 5



An intermediate of formula (XIX) and an intermediate of formula (XX) may be reacted in a suitable solvent such as, for example, dimethylsulfoxide, in the presence of a base

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such as, for example sodium hydroxide, to form an intermediate of formula (XV-a). The nitro moiety in the intermediates of formula (XV-a) may either be immediately reduced to an amino group using art-known reduction techniques such as, for example, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel, or may first be reacted with an intermediate of formula R^{4'}-W wherein R^{4'} is the same as R⁴ but other than hydrogen and W is a suitable leaving group such as, for example, a halogen, e.g. iodo, in a suitable solvent such as, for example, N,N-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, before reducing the nitro moiety.

10

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation such as, for example, those mentioned in WO99/02505 and the ones exemplified in the experimental part hereinafter.

15

The compounds of formula (I) may also be converted to the corresponding N-oxide forms following art-known procedures for converting a trivalent nitrogen into its N-oxide form. Said N-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

20

25

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angiitis, eosinophilic fasciitis, eosinophilic pneumonia,

PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.

The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergetically with eosinophils (Carr et al., 1994, Immunology, 91, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, Immunology Today, 15(3), 127-133).

The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, γ -interferon (IFN- γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

The selective chemokine inhibitory effect of the present compounds can be demonstrated by *in vitro* chemokine measurements in human blood. *In vivo* observations such as the inhibition of eosinophilia in mouse ear, the inhibition of blood eosinophilia in the *Ascaris* mouse model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA expression induced by anti-CD3 antibody in mice and the inhibition of allergen- or Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the usefulness of the present compounds in the treatment of eosinophil-dependent inflammatory diseases.

The present inhibitors of IL-5 production are particularly useful for administration via inhalation.

The intermediates of formula (XI-a) are interesting intermediates. Not only have they a particular usefulness as intermediates in the preparation of the compounds of formula (I), they also have valuable pharmacological activity.

In view of the above pharmacological properties, the compounds of formula (I) can be used as a medicine. In particular, the present compounds can be used in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned hereinabove, more in particular bronchial asthma, atopic dermatitis, 5 allergic rhinitis and allergic conjunctivitis.

In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from eosinophil-dependent inflammatory diseases, in particular bronchial asthma, atopic dermatitis, 10 allergic rhinitis and allergic conjunctivitis. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

15 The present invention also provides compositions for treating eosinophil-dependent inflammatory diseases comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

To prepare the pharmaceutical compositions of this invention, a therapeutically 20 effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as parenteral 25 administration; or topical administration such as via inhalation, a nose spray or the like. Application of said compositions may be by aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon, or without a propellant such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the 30 like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.

Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are

5 tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in

10 pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

15 Appropriate cyclodextrins are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6} alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β -CD; hydroxy C_{1-6} alkyl, particularly hydroxyethyl, hydroxy-

20 propyl or hydroxybutyl; carboxy C_{1-6} alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6} alkylcarbonyl, particularly acetyl; C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or carboxy- C_{1-6} alkyloxy C_{1-6} alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6} alkylcarbonyloxy C_{1-6} alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, randomly methylated β -CD,

25 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, 2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD (2-HP- β -CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two

30 cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10.

5

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges from 0.125 to 3.

10

Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the compounds of the present invention need to be labelled, in particular by replacing, partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having at least one ^{11}C -atom or tritium atom.

15

One particular group consists of those compounds of formula (I) wherein R^3 and/or R^4 are a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g. ^{122}I , ^{123}I , ^{125}I , ^{131}I ; radioactive bromides, e.g. ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br , and radioactive fluorides, e.g. ^{18}F . The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

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Another interesting form of radiolabelling is by substituting a carbon atom by a ^{11}C -atom or the substitution of a hydrogen atom by a tritium atom.

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Hence, said radiolabelled compounds of formula (I) can be used in a process of specifically marking receptor sites in biological material. Said process comprises the

steps of (a) radiolabelling a compound of formula (I), (b) administering this radio-labelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound. The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.

The radiolabelled compounds of formula (I) are also useful as agents for screening whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.

When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

In general, it is contemplated that a therapeutically effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

Experimental part

In the examples hereinafter, "DMSO" stands for dimethylsulfoxide, "RT" stands for room temperature, "DMF" stand for *N,N*-dimethylformamide, "EtOAc" stands for ethylacetate, "DIPE" stands for diisopropylether and "THF" stands for tetrahydrofuran.

A. Preparation of the intermediate compounds

Example A1

- a) A mixture of 2-chloropropionenitrile (0.2 mol) and 1,3-dichloro-5-nitrobenzene (0.2 mol) in DMSO (50ml) was added dropwise at RT to a solution of NaOH (1 mol) in DMSO (150ml) while the temperature was kept below 30°C. The mixture was stirred at RT for 1 hour, then poured out on ice and acidified with HCl. The precipitate was filtered off, washed with H₂O and taken up in CH₂Cl₂. The organic solution was washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 70/30). The pure fractions were collected and the solvent was evaporated, yielding 19.5 g (40%) of (±)-2,6-dichloro-α-methyl-4-nitrobenzeneacetonitrile (interm. 1).
- b) NaH 80% (0.0918 mol) was added portionwise at 0°C under N₂ flow to a solution of intermediate (1) (0.0612 mol) in DMF (100ml). The mixture was stirred at 0°C under N₂ flow for 1 hour. CH₃I (0.0918 mol) was added dropwise at 0°C. The mixture was stirred at 50°C for 12 hours, then poured out on ice and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated, yielding 17.1g of 2,6-dichloro-α,α-dimethyl-4-nitrobenzeneacetonitrile (interm. 2).
- c) A mixture of intermediate (2) (0.066 mol) in CH₃OH (200ml) was hydrogenated at RT under a 3 bar pressure for 1 hour with Raney Nickel (15g) as a catalyst. After uptake of H₂, the catalyst was filtered through celite, washed with CH₃OH and the filtrate was evaporated, yielding 17.1g of 4-amino-2,6-dichloro-α,α-dimethylbenzeneacetonitrile (interm. 3).

Example A2

- a) A solution of NaNO₂ (0.36 mol) in H₂O (50 ml) was added to a solution of intermediate (3) (0.34 mol) in acetic acid (700 ml) and HCl (102 ml), stirred at 10°C. The reaction mixture was stirred for 80 minutes at 10°C. A powdered mixture of sodium acetate (1.02 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.374 mol) was added and the reaction mixture was stirred for 40 minutes. The reaction mixture was poured out onto crushed ice. The precipitate was filtered off, washed with water, taken up into CH₂Cl₂, and the layers were separated. The organic layer was dried, filtered and the solvent evaporated, yielding 138.5 g (84%) of diethyl N,N'-

[2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]dicarbamate (interm. 4).

b) A solution of intermediate (4) (0.28 mol) and potassium acetate (0.28 mol) in acetic acid (1000 ml) was stirred and refluxed for 3 hours. The reaction mixture containing
5 ethyl [[2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 5) was used as such in the next step.

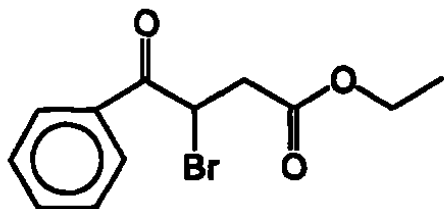
c) Intermediate (5) (crude reaction mixture) was treated with HCl 36% (0.84 mol). The reaction mixture was stirred and refluxed for 4 hours, then stirred at RT over the
10 weekend. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated, yielding 111.6 g of 2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 6).

d) A suspension of intermediate (6) (0.28 mol) in mercaptoacetic acid (250.0 ml) was
15 stirred for 4 hours at 100 °C, then allowed to cool to RT and stirred overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue was purified by short column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2). The
20 pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, then dried, yielding 36.8 g (41%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)- α,α -dimethylbenzeneacetonitrile. The filtrate was stirred in DIPE and the resulting precipitate was filtered off, washed with DIPE, and dried, yielding 2.5 g (3%) of 2,6-dichloro-4-(4,5-dihydro-
25 3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)- α,α -dimethylbenzeneacetonitrile (interm. 7).

e) A solution of intermediate (7) (0.107 mol) and *N,N*-bis(1-methylethyl)ethanamine (0.315 mol) in pyridine (500 ml) was stirred and heated to 80°C. H_2S was allowed to bubble through this solution for 24 hours at 80°C. H_2S gas inlet was stopped and the reaction mixture was stirred over the weekend at RT. The solvent was evaporated.
30 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (500 ml; 9:1) was added, and this mixture was poured out into 2 N HCl (1000 ml) at 0°C. The mixture was stirred for 10 minutes. The precipitate was filtered off and dried, yielding 23.2 g (64%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4)- α,α -dimethylbenzeneethanethioamide (interm. 8).

Example A3

Reaction under N₂ atmosphere. A solution of intermediate (8) (0.0125 mol) and



(0.0157 mol) in ethanol (60 ml) and DMF (30 ml;

dried over molecular sieves) was stirred for 6.5 hours at 60 °C, then overnight at RT.

- 5 The solvent was evaporated. The residue was taken up into water (100 ml) and this mixture was extracted with CH₂Cl₂ (100 ml). The separated organic layer was dried (MgSO₄), filtered and the solvent evaporated, then co-evaporated with toluene. The residue (13 g) was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 100/0, then 99/1, ending with 98/2). The desired fractions were
- 10 collected and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue (6.5 g) was crystallized from CH₃CN. The precipitate was filtered off, washed with CH₃CN and DIPE, then dried (vacuum, 50 °C), yielding 3.17 g (46.5 %) of ethyl-2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetate (intermediate 9) having a
- 15 melting point of 148°C.

Example A4

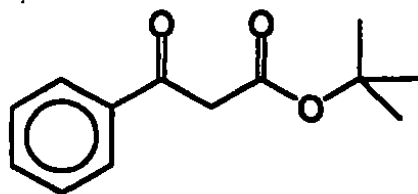
A mixture of intermediate (9) (0.00183 mol) and NaOH 1N (0.0055 mol) in CH₃OH (25 ml) and THF (25 ml) was stirred overnight at RT. The reaction mixture was

- 20 acidified with 1N HCl (8 ml), and the product was taken up into EtOAc. The organic layer was washed with brine, dried, filtered and the solvent was evaporated. The residue was crystallized from CH₃CN. The precipitate was filtered off, washed with DIPE, and dried, yielding 0.8 g (79%) of 2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetic acid
- 25 (intermediate (10)).

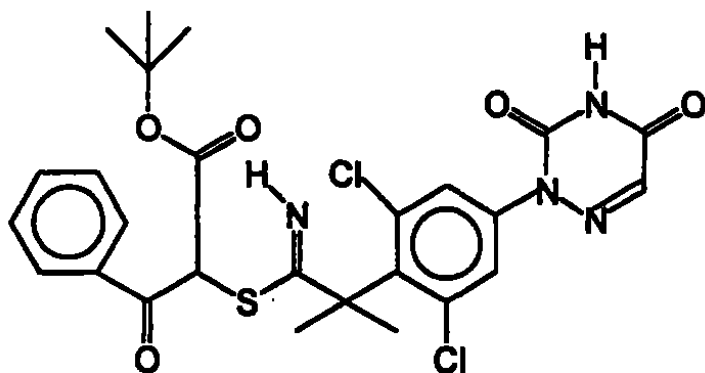
Example A5

First a solution of bromine (0.02 mol) in CH₂Cl₂ (20 ml) was added dropwise at 10°C under N₂ flow to a mixture of a compound of formula

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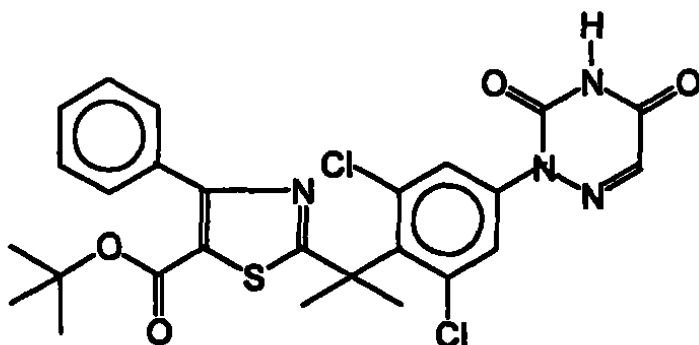
- (0.0227 mol) in CH_2Cl_2 (50ml). The mixture was stirred at 10°C for 1 hour. H_2O and solid K_2CO_3 were added. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The reaction was carried out 4 times, using the same quantities and combining the residues yielding 14 g (51%) of 1,1-dimethylethyl α -bromo- β -oxo-benzenepropanoate. A mixture of intermediate (8) (0.0119 mol), 1,1-dimethylethyl α -bromo- β -oxo-benzenepropanoate (0.0137 mol) and K_2CO_3 (0.0357 mol) in CH_3CN (55ml) was stirred at room temperature for 3.5 hours. Ice and EtOAc were added. The mixture was acidified with HCl 3N. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The product was used without further purification. Yielding: 8g of intermediate 11 having the formula



20 Example A6

- Intermediate (11) (0.0119 mol) and tert.-butanol (24g) were stirred and refluxed for 2 hours. The mixture was brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . The organic solution was washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (7.8g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1; 15-40 μm). Two fractions were collected and their solvents were evaporated. Yielding: 2.66g (fraction 1) and 0.7g fraction 2 (50%). Fraction 2 was purified by column chromatography over C 18 (eluent: $\text{CH}_3\text{OH}/\text{NH}_4\text{OAc}$ 0.5% 80/20; column: HYPERSIL C 18 3 μm). The pure fractions were collected and the solvent was

evaporated. Yielding: 0.45g of intermediate 12 having a melting point of 130°C and represented by the formula

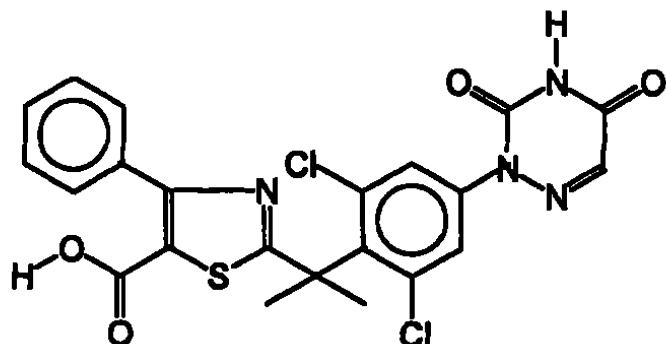


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Example A7

Intermediate 12 (0.00465 mol) was added portionwise at 0°C-10°C to trifluoroacetic acid (35ml). The mixture was stirred at room temperature for 3 hours and poured out into H₂O. The precipitate was filtered off, washed with H₂O and taken up in CH₂Cl₂.

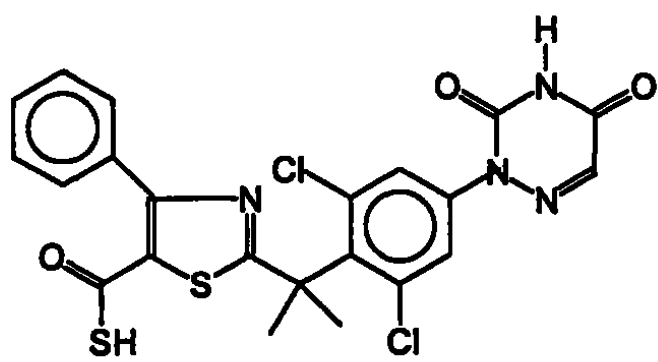
- 10 The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.4g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 97/3/0.2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN. The precipitate was filtered off and dried. Yielding: 1.16g of intermediate 13 having a melting point of 232°C and represented by the formula
- 15



Example A8

1,1'-carbonylbis-1H-imidazole (0.0159 mol) was added portionwise at RT under N₂ flow to a solution of intermediate (13) (0.00795 mol) in DMF (60 ml). The mixture was stirred at RT overnight. H₂S was bubbled through the mixture for 1 hour. The mixture was stirred at RT for 1 hour, poured out into a saturated NaCl solution and

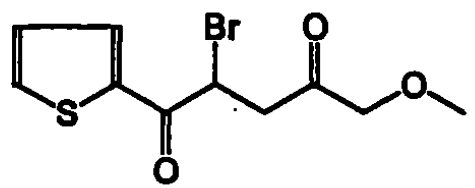
extracted twice with CH₂Cl₂. The combined organic layer was dried (MgSO₄), filtered and the solvent was evaporated. The product, interm. 14 represented by the formula



5 was used without further purification.

Example A9

A mixture of intermediate (8) (0.0158 mol) and

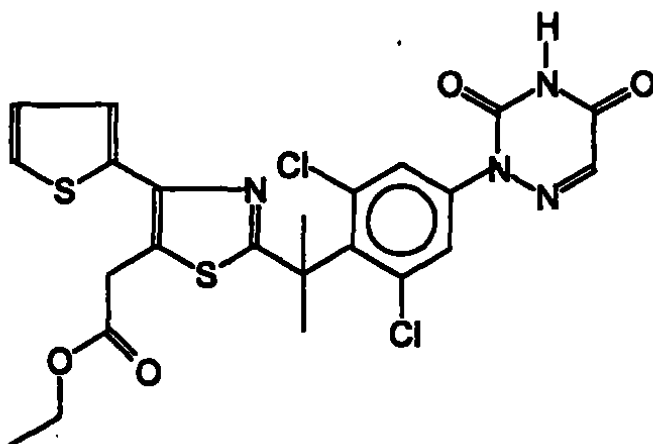


10 (0.0237 mol) in ethanol (60ml) and DMF (40ml)

was stirred at 60°C for 4 hours. The solvent was evaporated. EtOAc was added. The organic solution was washed 3 times with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. The residue (11.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. Yielding: 4.2g (47%). Part of this fraction (1.5g) was crystallized from petroleum ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.15g of intermediate 15 having a melting point of 126°C and represented by the formula

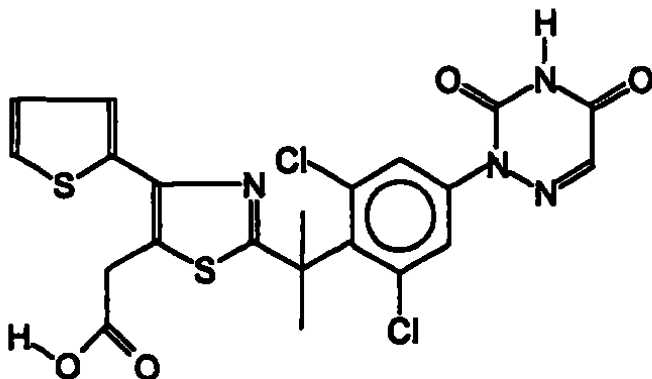
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10 Example A10

A mixture of intermediate (15) (0.0045 mol) and NaOH (0.0135 mol) in methanol (30ml) and THF (30ml) was stirred at room temperature for 12 hours, poured out on ice, acidified with HCl and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.5g (64%). Part of this fraction (1g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.5g of intermediate 16 having a melting point of 192°C and represented by the formula



20 Example A11

a) NaOCH₃, 30% (0.592 mol) was added to a solution of hydroxylamine hydrochloride (0.1085 mol) in CH₃OH (200 ml), stirred at RT. The mixture was stirred for 10 minutes. Intermediate (3) (0.0542 mol) was added portionwise and the resulting reaction mixture was stirred and refluxed overnight. The solvent was evaporated. The residue was partitioned between CH₂Cl₂ and water. The organic layer was separated,

dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, and dried, yielding 3.7 g of (26%) 4-amino-2,6-dichloro-*N*'-hydroxy- α,α -dimethylbenzeneethanimidamide (interm. 17).

b) A solution of intermediate (17) (0.0323 mol) and *N,N*-bis(methylethyl)ethanamine (0.0339 mol) in CH_2Cl_2 (190 ml) was stirred at 15°C. A solution of 2-methylbenzoyl chloride (0.0323 mol) in CH_2Cl_2 (10 ml) was added dropwise and the resulting reaction mixture was stirred for one hour. Water was added. The organic layer was separated, dried, filtered and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 13.0 g of [1-amino-2-(4-amino-2,6-dichlorophenyl)-2-methylpropylidenyl]amino 2-methylbenzoate (interm. 18).

c) A solution of intermediate (18) (0.0323 mol) and *p*-toluenesulfonic acid (0.0323 mol) in DMSO (100 ml) was stirred for 30 minutes at 150°C. The reaction mixture was cooled. Water was added and this mixture was extracted with toluene. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2). The desired fractions were collected and the solvent was evaporated. The concentrate was co-evaporated with EtOAc, yielding 11.7 g of 3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]benzenamine (interm. 19).

d) A solution of intermediate (19) (0.0302 mol) and HCl conc. (0.0906 mol) in acetic acid (100 ml) was stirred at 0°C. A solution of NaNO_2 (0.032 mol) in water (10 ml) was added dropwise at 0°C. The reaction mixture was stirred for 1 hour at 0°C. A powdered mixture of sodium acetate (0.0906 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.0332 mol) was added portionwise. The mixture was allowed to warm to RT and stirred for 1 hour. Water was added and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated, yielding diethyl *N,N*'-[2-[[3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]-dicarbamate (interm. 20).

e) A solution of intermediate (20) (0.0302 mol) and sodium acetate (0.0302 mol) in acetic acid (200 ml) was stirred and refluxed for 3 hours. The reaction mixture was poured out into water and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding ethyl [[2-[3,5-dichloro-4-[1-[5-(2-methyl-

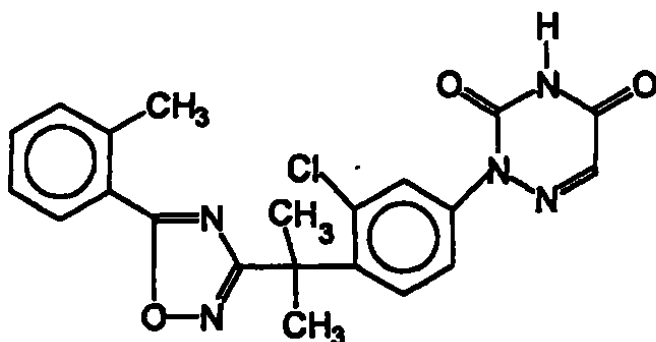
-36-

phenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 21).

f) A mixture of intermediate (21) (0.0302 mol) in HCl 36% (10 ml) and acetic acid (200 ml) was stirred and refluxed overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated, yielding 16.3 g of 2-[3,5-dichloro-4-[1-[5-[2-methylphenyl]-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 22).

Example A12

A mixture of intermediate (22) (0.0133 mol) in mercaptoacetic acid (7ml) was stirred at 175°C for 2 hours. The mixture was cooled, poured out into ice water, basified with K_2CO_3 and extracted with EtOAc. The organic layer was separated, washed with H_2O , dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1). The pure fractions were collected and the solvent was evaporated, yielding 2.2g (36%) of intermediate 23 represented by the formula

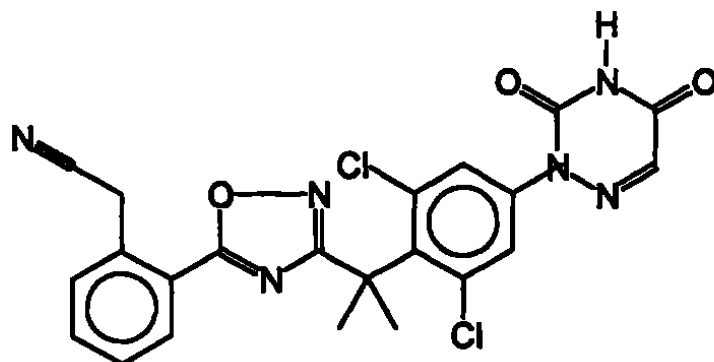


Example A13

A mixture of intermediate (23) (0.0011 mol), 1-bromo-2,5-pyrrolinedione (0.0011 mol) and dibenzoyl peroxide (catalytic quantity) in CCl_4 (30 ml) was stirred and refluxed for 3 hours. The mixture was allowed to cool to RT. The mixture was filtered over dicalite and the filtrate contained 2-[4-[1-[5-[2-(bromomethyl)phenyl]-1,2,4-oxadiazol-3-yl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (intermediate 24).

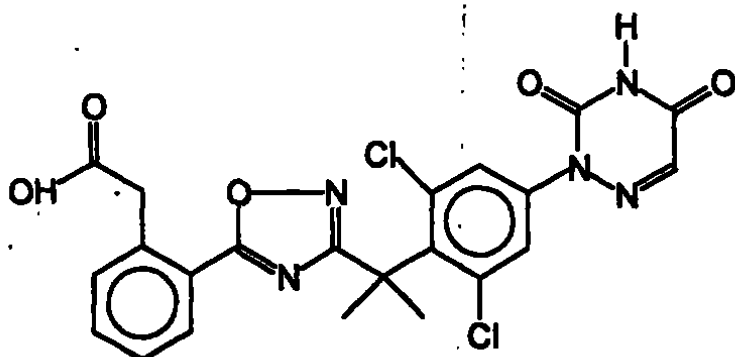
Example A14

A solution of intermediate (24) (0.017 mol) and KCN (0.034 mol) in ethanol (100 ml) and H₂O (30 ml) was stirred for 8 hours at 60°C. The solvent was evaporated under reduced pressure. The residue was taken up into CH₂Cl₂, then washed with water, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 8.2 g of interm.25 represented by the formula

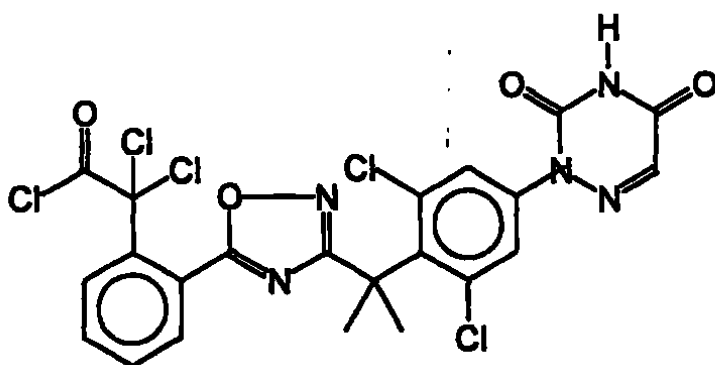
**Example A15**

A solution of intermediate (25) (0.017 mol) in HOAc (50 ml), H₂SO₄ (50 ml) and H₂O (50 ml) was stirred and refluxed for 2 hours. The reaction mixture was poured out into ice-water and the resulting precipitate was filtered off, washed, then dissolved in CH₂Cl₂. The organic solution was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 95/5). The desired fractions were collected and the solvent was evaporated. The residue was purified by HPLC over RP BDS Hyperprep C18 (100 Å =, 8 µm; gradient elution with (0.5% NH₄OAc in water/CH₃CN 90/10)/CH₃OH/CH₃CN). The pure fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off and dried (vacuum, 60 °C). Yield: 0.084 g of intermediate 26 represented by the formula

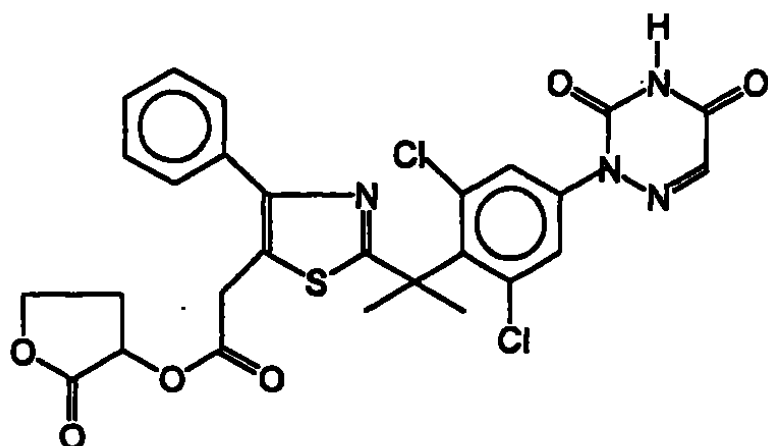
-38-

**Example A16**

A solution of intermediate (26) (0.0014 mol) in SOCl₂ (15 ml) was stirred and refluxed for 1 hour. SOCl₂ was evaporated under reduced pressure. Toluene was added and azeotroped on the rotary evaporator, yielding 100% of intermediate 27 represented by the formula

**B. Preparation of the final compounds****Example B1**

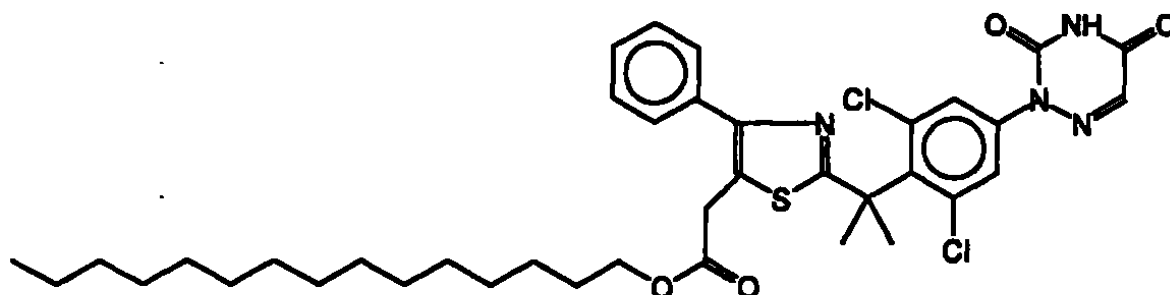
A mixture of 3-bromodihydro-2(3H)-furanone (0.0081 mol) in DMF (16ml) was added dropwise at room temperature to a mixture of intermediate (10) (0.00773 mol) and NaHCO₃ (0.0081 mol) in DMF (30ml). The mixture was stirred at 70°C for 5 hours and brought to room temperature. H₂O and a saturated NaCl solution were added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried. Yielding: 1.24g compound 1 having a melting point of 72°C and represented by the formula



Example B2

A solution of 1-bromopentadecane (0.0051 mol) in DMF (18ml) was added dropwise at room temperature to a mixture of intermediate (10) (0.00483 mol) and NaHCO_3

- 5 (0.0051 mol) in DMF (10ml). The mixture was stirred at 70°C for 5 hours and at 45°C overnight, then brought to room temperature. H₂O and NaCl was added. The mixture was extracted with EtOAc. The organic layer was separated, washed with a saturated NaCl solution, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3.8g) was purified by column chromatography over silica gel (eluent:
10 CH₂Cl₂/CH₃OH 98/2; 15–40 µm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.49g compound 2 having a melting point of 80°C and represented by the formula

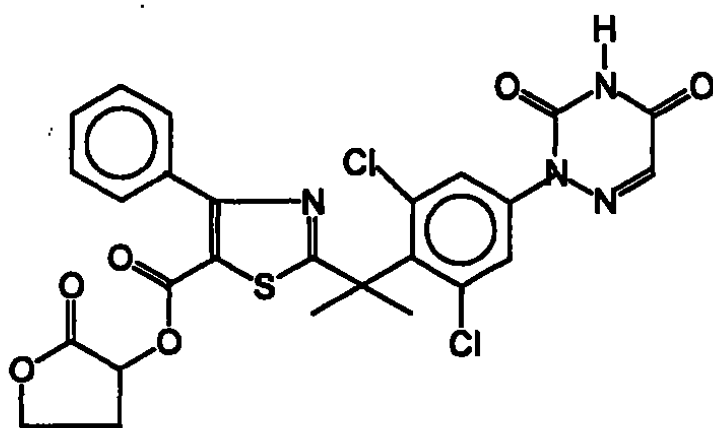


Example B3

- 15 A solution of 3-bromodihydro-2(3H)-furanone (0.0073 mol) in DMF (12ml) was added dropwise at RT to a mixture of intermediate (13) (0.00695 mol) and NaHCO₃ (0.0073 mol) in DMF (22ml). The mixture was stirred at 70°C for 2.5 hours, brought to RT and poured out into H₂O. The precipitate was filtered off and taken up in CH₂Cl₂. The organic layer was separated, washed with H₂O, dried (MgSO₄), filtered and the solvent
20 was evaporated. The residue (5.4g) was purified by column chromatography over silica

-40-

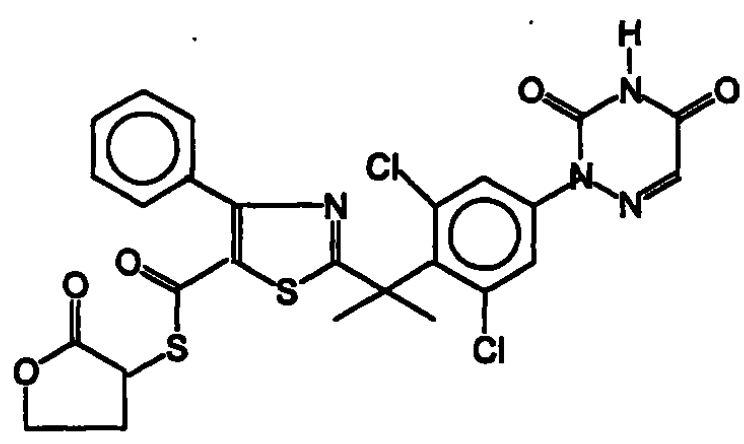
gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μ m). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN, diethyl ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.3g. This fraction was recrystallized from CH₃CN, 2-propanone and diethyl ether. The precipitate was
5 filtered off and dried. Yielding: 0.89g compound 3 having a melting point of 208°C and represented by the formula



Example B4

NaHCO₃ (0.00835 mol) was added dropwise at 5°C under N₂ flow to a mixture of
10 intermediate (14) (0.00795 mol) in DMF (22ml). Then a solution of 3-bromodihydro-2(3H)-furanone (0.00835 mol) in DMF (12ml) was added dropwise. The mixture was brought to RT and stirred at RT for 30 min and then poured out into H₂O and a saturated NaCl solution. A small amount of HCl 3N was added. The precipitate was filtered off and taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄),
15 filtered and the solvent was evaporated. The residue (5.1g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 μ m). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN, diethyl ether and DIPE. The precipitate was filtered off and dried. The residue was recrystallized from CH₃CN, diethyl ether and DIPE. The
20 precipitate was filtered off and dried. Yielding: 0.85g compound 4 having a melting point of 212°C and represented by the formula

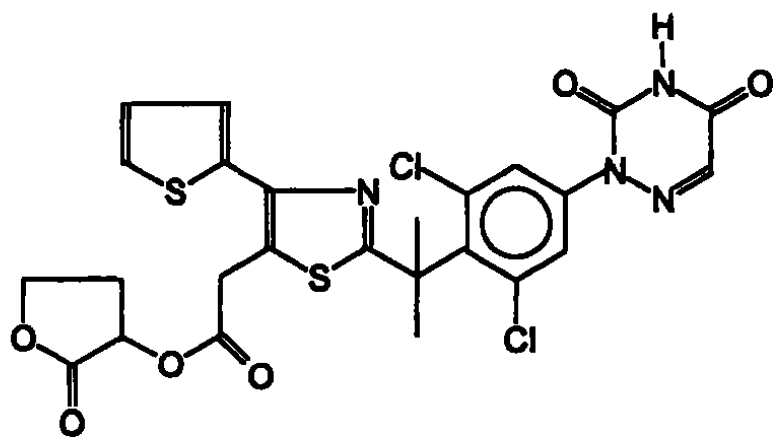
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Example B5

5 A mixture of 3-bromodihydro-2(3H)-furanone (0.00172 mol) in DMF (5ml) was added dropwise at RT to a mixture of intermediate (16) (0.00172 mol) and NaHCO₃ (0.00172 mol) in DMF (5ml). The mixture was stirred at 70°C for 5 hours, poured out into H₂O and a saturated NaCl solution and extracted with EtOAc. The organic layer was separated, washed several times with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The desired fractions were collected and

10 the solvent was evaporated. The residue was purified again by column chromatography over silica gel (eluent: CH₂Cl₂/2-propanol 97/3; 15-40 μm). The desired fractions were collected and the solvent was evaporated. Yielding: 0.13g compound 5 having a melting point of 110°C and represented by the formula

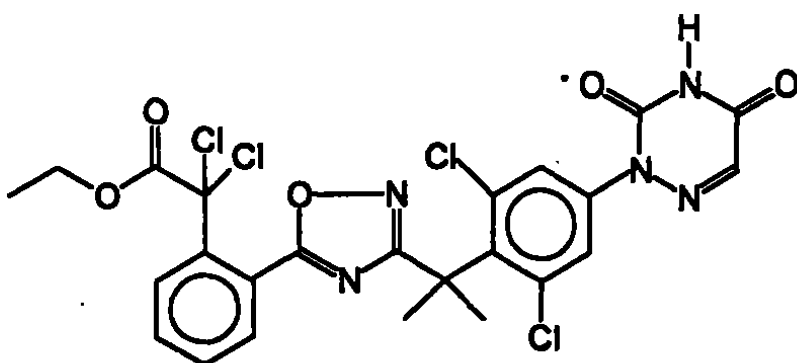


15 Example B6

A solution of intermediate (27) (0.001 mol) in ethanol (15 ml) and dichloromethane (15 ml) was stirred and refluxed for one hour. The solvent was evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with water, dried (MgSO₄),

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filtered and the solvent was evaporated. The residue was purified by HPLC over Hyperprep C18 (eluent: ((0.5% NH₄OAc in H₂O)/CH₃CN 90/10)/CH₃CN (0 min) 80/20, (44 min) 20/80, (57-61 min) 0/100). The desired fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off, washed and dried (vacuum, 60 °C). Yield: 0.059 g compound 6 having a melting point of 157°C and represented by the formula

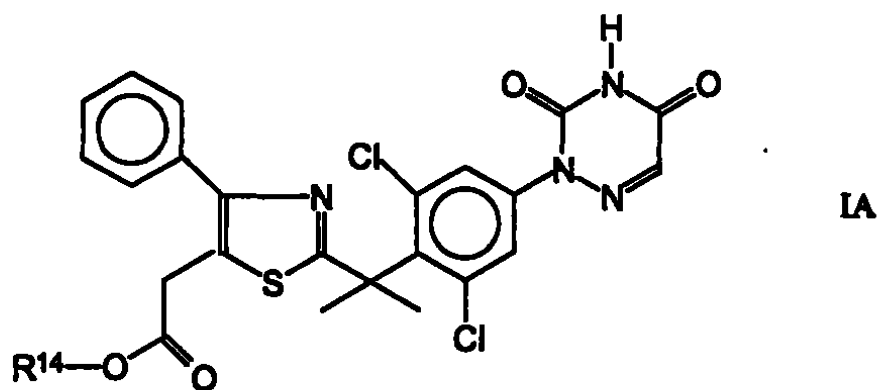


Example B7

A mixture of intermediate (10) (0.00387 mol) and 1,1'-carbonylbis-1H-imidazole (0.0058 mol) in dichloromethane (40ml) was stirred at RT for 90 minutes, then cyclohexylmethanol (0.0058 mol) was added. The mixture was stirred at RT overnight, diluted with CH₂Cl₂ and washed twice with an aqueous solution of NaCl. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 50/50). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate was filtered off, washed with DIPE and dried at 50°C overnight. Yielding: 1.43g compound 7 with a melting point of 180°C and represented by the formula

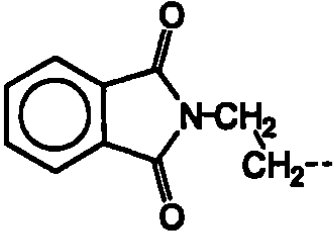
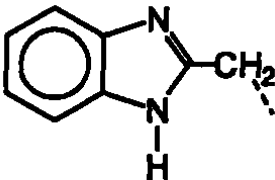
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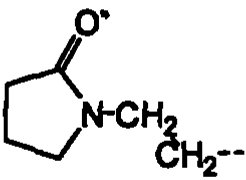
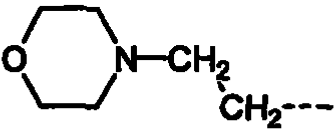


wherein R¹⁴ is cyclohexylmethyl.

The following table 1 lists compounds of formula (1A) which were prepared according to the same procedure.

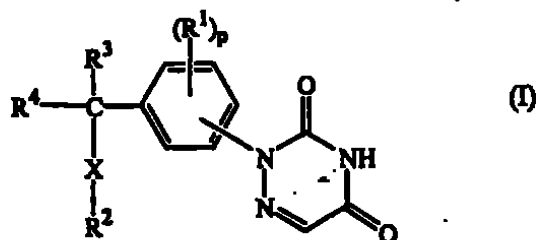
COMPOUND NO.	R ¹⁴	MELTING POINT (°C)
8		
9	Isopentyl	148
10	2-phenyl-ethyl	130
11	3-phenyl-n-propyl	114
12	2-(N,N'-diisopropylamino)-ethyl	136
13	2-cyano-ethyl	179
14		
15	3-cyclohexyl-n-propyl	130

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16	4-phenyl-n-butyl	128
17	Cyclopropylmethyl	
18	3-cyclopropyl-n-propyl	
19		
20		

Claims

1. A compound having the formula



a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR⁵ or a direct bond or *X*-R² taken together may represent cyano;

Y represents O, S, NR⁵, or S(O)₂;

each R¹ independently represents C(=O)-Z-R¹⁴, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl,

hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or C₁₋₄alkyl substituted with C(=O)-Z-R¹⁴, Het³, R⁶ or NR⁷R⁸;

R² represents Het¹, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkyl or C₁₋₆alkyl substituted with one or two substituents selected from C(=O)-Z-R¹⁴, hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylsulfonyloxy, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if *X* is O, S or NR⁵, then R² may also represent aminothiocarbonyl, C₁₋₄alkylcarbonyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₄alkylthiocarbonyl optionally substituted with C(=O)-Z-R¹⁴, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl;

R³ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl;

R⁴ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; or

R³ and R⁴ taken together form a C₂₋₆alkanediyl;

R⁵ represents hydrogen or C₁₋₄alkyl;

each R⁶ independently represents C₁₋₆alkylsulfonyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)-aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl, phenylC₁₋₄alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C₁₋₄alkyl-*N*-piperidinylaminosulfonyl or mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkylsulfonyl;

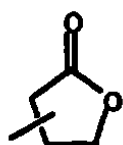
each R^7 and each R^8 are independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, arylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³, Het⁴ and R^6 ;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³, Het⁴ and R^6 ;

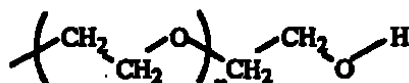
each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4} alkyloxy optionally substituted with C(=O)-Z- R^{14} , formyl, trihalo C_{1-4} alkylsulfonyloxy, R^6 , NR^7R^8 , C(=O) $NR^{15}R^{16}$, -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , aryl, aryloxy, arylcarbonyl, C_{3-7} cycloalkyl optionally substituted with C(=O)-Z- R^{14} , C_{3-7} cycloalkyloxy optionally substituted with C(=O)-Z- R^{14} , phthalimide-2-yl, Het³ and C(=O)Het³;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} and R^6 ;

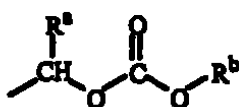
each R^{14} independently represents C_{1-4} alkyl substituted with one or more substituents selected from phenyl, di- C_{1-4} alkylamino, cyano, Het¹ and C_{3-7} cycloalkyl, hydrogen, C_{1-20} acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C_{1-20} alkyl, C_{3-7} cycloalkyl, polyhalo C_{1-20} alkyl or a radical of formula



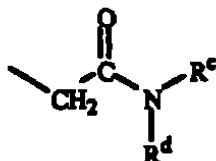
(a)



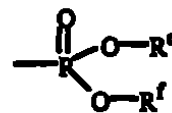
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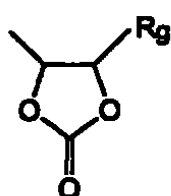
(c)



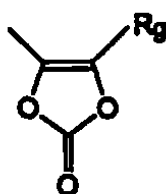
(d)



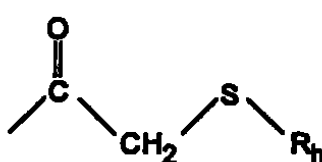
(e)



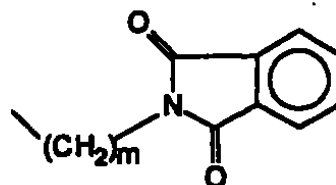
(h)



(i)



(j)



(k)

wherein n is 0 to 5 and m is 1 to 4;

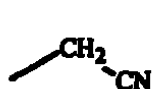
R^a, R^b, R^c, R^d, R^e and R^f are each independently hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; or

R^e and R^f taken together may form -CH₂-CH₂-, -CH₂-CH₂-CH₂- or -CH₂-CH₂-CH₂-CH₂-;

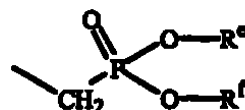
R_g and R_h are each independently C₁₋₄ alkyl;

each Z independently represents O, S, NH, -CH₂-O- or -CH₂-S- whereby -CH₂- is attached to the carbonyl group;

-Z-R¹⁴ taken together form a radical of formula



(f)



(g)

R¹⁵ and R¹⁶ are each independently selected from dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl,

C₁₋₄alkyloxyC₁₋₄alkyl, -C(=O)-Z-R¹⁴, arylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, pyridinylC₁₋₄alkyl, Het³, Het⁴ or R⁶;

aminocarbonylmethylene or mono- or di(C₁₋₄alkyl)aminocarbonylmethylene;

aryl represents phenyl optionally substituted with one, two or three substituents each

independently selected from nitro, azido, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cyclo-

alkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-Z-R¹⁴, R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³ or NR⁹R¹⁰;

- 5 Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, 10 trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]-thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from 15 Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het² and R¹¹;

- Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, 20 dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolyl, 25 phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het⁴, R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het⁴ and R¹¹;

- 30 Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl,

C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, $C(=O)-Z-R^{14}$, R^6 and C_{1-4} alkyl substituted with one or two substituents independently selected from hydroxy,

C_{1-4} alkyloxy, phenyl, $C(=O)-Z-R^{14}$, $-Y-C_{1-4}$ alkanediyl- $C(=O)-Z-R^{14}$, R^6 and $NR^{12}R^{13}$;

Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, -

5 triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl provided however that

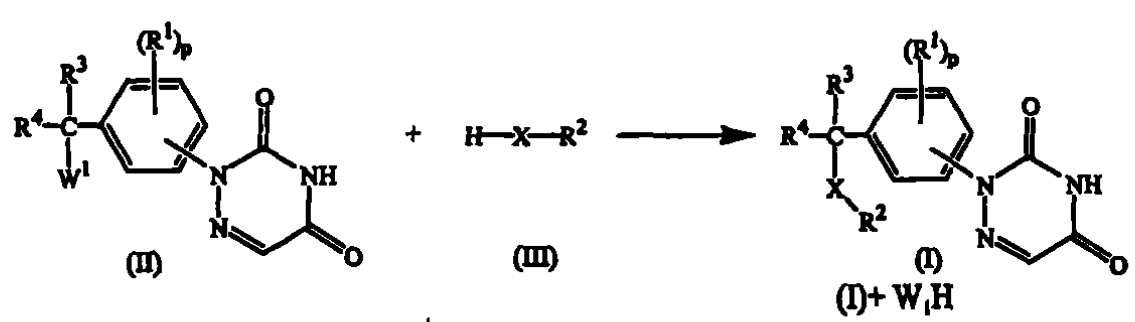
- R^2 is other than C_{1-4} alkyloxycarbonyl C_{1-4} alkyl, aminocarbonyl; and
- R^7 , R^8 , R^9 and R^{10} are other than aminocarbonyl, C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonylcarbonyl $C(=O)-O-R^{14}$, C_{1-4} alkanediyl $C(=O)-O-R^{14}$ and $-Y-C_{1-4}$ alkanediyl $C(=O)-O-R^{14}$; and
- R^{12} and R^{13} are other than C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylcarbonyl; and
- R^{11} is other than $C(=O)-O-R^{14}$, $Y-C_{1-4}$ alkanediyl - $C(=O)-OR^{14}$, $C(=O)NH_2$, $C(=O)NHC_{1-4}$ alkyl or $C(=O)NHC_{1-7}$ cycloalkyl; and
- R^{14} is other than hydrogen, C_{1-4} alkyl, C_{1-7} cycloalkyl, aminocarbonylmethylene, mono- or di (C_{1-4} alkyl) aminocarbonylmethylene in the event Z is 0; and
- R^{15} and R^{16} are other than aminocarbonyl, C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl or C_{1-4} alkyloxycarbonylcarbonyl; and
- Aryl is other than phenyl substituted with $C(=O)-O-R^{14}$, $C(=O)NH_2$, $C(=O)NHC_{1-4}$ alkyl, $C(=O)NHC_{1-7}$ cycloalkyl and/or with C_{1-4} alkyl substituted with $C(=O)-O-R^{14}$ or $Y-C_{1-4}$ alkanediyl - $C(=O)-O-R^{14}$; and
- Het³ is other than a monocyclic heterocycle substituted with $C(=O)-O-R^{14}$ and/or with C_{1-4} alkyl substituted with $C(=O)-O-R^{14}$ and/or $Y-C_{1-4}$ alkanediyl - $C(=O)-O-R^{14}$; and
- The said compound of formula (I) contains at least one - $C(=O)-Z-R^{14}$ moiety.

2. A compound as claimed in claim 1 wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X- R^2 , R^3 and R^4 substituents.

3. A compound as claimed in claims 1 or 2 wherein R^2 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, wherein said monocyclic

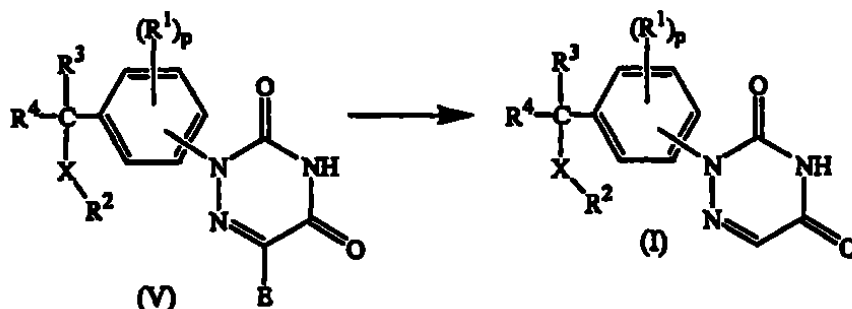
heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹.

- 5 4. A compound as claimed in any one of claims 1 to 3 wherein R³ and R⁴ are both methyl and -X-R² is Het¹.
5. A compound as claimed in any one of claims 1 to 4 wherein p is 1 or 2 and each R¹ is chloro.
- 10 6. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.
- 15 7. A process for preparing a composition as claimed in claim 6, , wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 5.
8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.
- 20 9. Use of a compound as claimed in any one of claims 1 to 5 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases.
10. A process for preparing a compound as claimed in claim 1, characterized by,
25 a) reacting an intermediate of formula (II) wherein W¹ is a suitable leaving group with an appropriate reagent of formula (III) optionally in a reaction-inert solvent and optionally in the presence of a base at a temperature ranging between - 70°C and reflux temperature;



wherein R^1 , R^2 , R^3 , R^4 , p and X are as defined in claim 1 or;

b) eliminating the group E of a triazinedione of formula (V)



wherein E is an appropriate electron attracting group and R^1 , R^2 , R^4 , X and p are as defined in claim 1;

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and also, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

11. A process of marking a receptor comprising the steps of

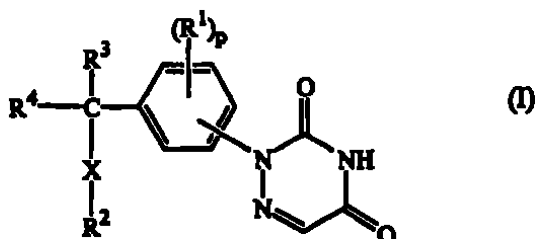
- a) radiolabelling a compound as defined in claim 1;
- b) administering said radiolabelled compound to biological material,
- c) detecting the emissions from the radiolabelled compound.

12. A process of imaging an organ, characterized by, administering a sufficient amount of a radiolabelled compound of formula (I) in an appropriate composition, and detecting the emissions from the radioactive compound.

ABSTRACTNON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

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The present invention is concerned with the compounds of formula



the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein *p* is 0 to 4; *X* is O, S, NR⁵ or a direct bond; *Y* is O, S, NR⁵ or S(O)₂; R¹ independently is C(=O)-Z-R¹⁴, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, NR⁷R⁸ or substituted C₁₋₄alkyl; R² is Het¹, C₃₋₇cycloalkyl or optionally substituted C₁₋₆alkyl and if *X* is O, S or NR⁵, then R² may also represent C(=O)-Z-R¹⁴, aminothiocarbonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; R³ and R⁴ independently are hydrogen, C₁₋₄alkyl or C₃₋₇cycloalkyl or R³ and R⁴ together form a C₂₋₆alkanediyl; R⁵ is hydrogen or C₁₋₄alkyl; R⁷ and R⁸ are independently hydrogen, optionally substituted C₁₋₄alkyl, aryl, a carbonyl containing moiety, C₃₋₇cycloalkyl, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴ or Het³; R¹⁴ is hydrogen, C₁₋₂₀alkyl, C₃₋₇cycloalkyl, C₁₋₂₀acyl or another radical; *Z* is O, S, NH, -CH₂O- or -CH₂S- whereby -CH₂- is attached to the carbonyl group; aryl is optionally substituted phenyl; Het¹, Het², Het³ and Het⁴ are optionally substituted heterocycles, provided that the said compounds contain at least one -C(=O)-Z-R¹⁴ moiety; to processes for their preparation and pharmaceutical compositions comprising them. It further relates to their use as a medicine.

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Janssen Pharmaceutica N.V. C-JAB1520-COL

REF: LLC-074-2000. La presente es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial).

OFICINA EUROPEA DE PATENTES

CERTIFICADO

Los documentos adjuntos son fiel copia de la solicitud de patente Europea según la descripción que aparece en la siguiente página, presentada originalmente.

No. de Solicitud de la Patente 99126035.7

El Presidente de la Oficina Europea de Patentes

I.L.C. HATTEN-HECKMAN

(Firmado)

LA HAYA, 23 / 08 / 00

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GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

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OFICINA EUROPEA DE PATENTES

Solicitud No.: 89126035.7
Fecha de Presentación: 27 / 12 / 99

Solicitante:

JANSSEN PHARMACEUTICA N.V.

2340 Beerse

BELGIUM

Título del Invento:

Inhibidores no esteroides IL-5, procesos para su
preparación y las composiciones farmacéuticas que los
contiene.

País: EP Fecha: 06/08/99 Archivo No.: EPA 99870170

Clasificación Internacional de la Patente:

Estados Contratantes Designados en la Fecha de la
Presentación:

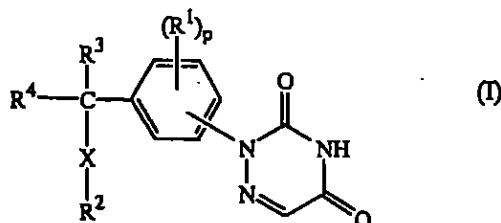
AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE

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REIVINDICACIONES

27-12-1999 EP99126035.7

1. Un compuesto que tiene la siguiente formula:



un N-óxido, una sal de adición farmacéuticamente aceptable o una de sus formas estereoquímicamente isoméricas, donde:

p representa un entero que es 0, 1, 2, 3 o 4;

X representa O, S, NR⁵ o un enlace directo o -X-R² tomados conjuntamente pueden representar ciano;

Y representa O, S, NR⁵, o S(O)₂;

cada R¹ independientemente representa C(=O)-Z-R¹⁴, alquilo C₁₋₈, halo, polihaloC₁₋₈alquilo, hidroxilo, mercapto, alquilo C₁₋₈oxi, alquiltio C₁₋₈, alquilcarbonilo C₁₋₈, arilo, ciano, nitro, Het³, R⁶, NR⁷R⁸ o alquilo C₁₋₄ sustituido por C(=O)-Z-R¹⁴, Het³, R⁶ o NR⁷R⁸;

R² representa Het¹, cicloalquilo C₃₋₇ sustituido opcional por C(=O)-Z-R¹⁴, alquilo C₁₋₈ o alquilo C₁₋₈ sustituido por uno o dos sustitutos que se seleccionan a partir de C(=O)-Z-R¹⁴, hidroxilo, ciano, amino, mono- o di(alquilo C₁₋₄)amino, alquilo C₁₋₈oxi sustituido opcionalmente por C(=O)-Z-R¹⁴, alquilsulfonilo C₁₋₈, cicloalquilo C₃₋₇ sustituido opcionalmente por C(=O)-Z-R¹⁴, arilo, arilo C₁₋₈oxi, ariltio, Het¹, Het¹oxi y Het¹tio; y si X es O, S, o NR⁵, entonces R² puede también representar el aminotiocarbonilo, alquilcarbonilo C₁₋₄ sustituido opcionalmente por C(=O)-Z-R¹⁴, alquiltiocarbonilo

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C₁₋₄ sustituido opcionalmente por C(=O)-Z-R¹⁴, arilcarbonilo, ariltiocarbonilo, Het¹carbonilo o Het¹tiocarbonilo;

R³ representa hidrógeno, alquilo C₁₋₈ o cicloalquilo C₃₋₇;

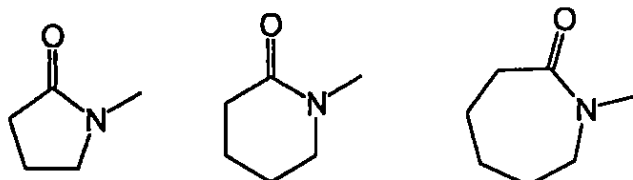
R⁴ representa hidrógeno, alquilo C₁₋₈ o cicloalquilo C₃₋₇; o

R³ y R⁴ tomados conjuntamente forman un alcanediilo C₂₋₈;

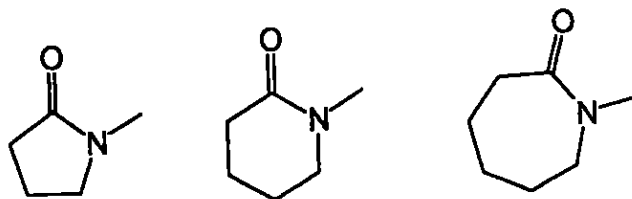
R⁵ representa hidrógeno o alquilo C₁₋₄;

cada R⁶ independientemente representa el alquilsulfonilo C₁₋₈, aminosulfonilo, mono- o di(alquilo C₁₋₄)-aminosulfonilo, mono- o di(benzil)aminosulfonilo, polihaloC₁₋₈alquilsulfonilo, alquilsulfinilo C₁₋₈, fenilC₁₋₄alquilsulfonilo, piperazinilsulfonilo, aminopiperidinilsulfonilo, piperidinilaminosulfonilo, N-alquilo C₁₋₄-N-piperidinilaminosulfonilo o mono-o di(alquilo C₁₋₄)aminoC₁₋₄alquilsulfonilo;

cada R⁷ y cada R⁸ se seleccionan independientemente a partir del hidrógeno, alquilo C₁₋₄, hidroxialquilo C₁₋₄, dihidroxialquilo C₁₋₄, arilo, arilC₁₋₄alquilo, alquilo C₁₋₄alquilo, alquilo C₁₋₄alquilo, alquilcarbonilo C₁₋₄, arilcarbonilo, Het³carbonilo, mono- o di(alquilo C₁₋₄)aminoC₁₋₄alquilo, arilaminocarbonilo, arilaminotiocarbonilo, Het³aminocarbonilo, Het³aminotiocarbonilo, cicloalquilo C₃₋₇, piridinilC₁₋₄alquilo, alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, Het³, Het⁴ y R⁶; o R⁷ y R⁸ tomados junto con el átomo de nitrógeno al cual se adhieren forman un radical de la siguiente formula:



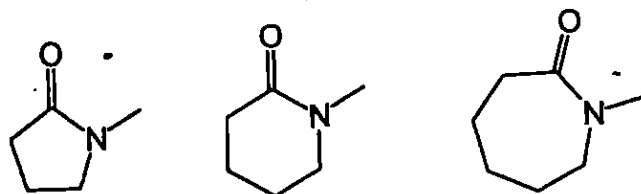
R^9 y R^{10} se seleccionan cada uno independientemente del hidrógeno, alquilo C_{1-4} , hidroxialquilo, dihidroxialquilo, fenilo, fenilalquilo, alquiloalquilo, alquiloalquilo, alquilcarbonilo C_{1-4} , fenilcarbonilo, Het³carbonilo, mono- o di(alquilo C_{1-4})aminoalquilo, fenilaminocarbonilo, fenilaminotiocarbonilo, Het³aminocarbonilo, Het³aminotiocarbonilo, cicloalquilo C_{3-7} , piridinilalquilo, alcanedilo $C_{1-4}-C(=O)-Z-R^{14}$, $-C(=O)-Z-R^{14}$, $-Y-$ alcanedilo $C_{1-4}-C(=O)-Z-R^{14}$, Het³, Het⁴ y R^8 ; o R^9 y R^{10} tomados junto con el átomo de nitrógeno al cual se adhieren forman un radical de la siguiente formula:



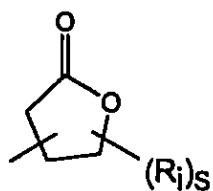
cada R^{11} independientemente se selecciona del hidroxil, mercapto, ciano, nitro, halo, trihalometilo, alquiloalquilo C_{1-4} sustituido opcionalmente por $C(=O)-Z-R^{14}$, formilo, trihaloalquiloalquiloalquilo, R^8 , NR^7R^8 , $C(=O)NR^{15}R^{16}$, $-C(=O)-Z-R^{14}$, $-Y-$ alcanedilo $C_{1-4}-C(=O)-Z-R^{14}$, arilo ariloalquilo, arilcarbonilo, cicloalquilo C_{3-7} sustituido opcionalmente por $C(=O)-Z-R^{14}$, cicloalquiloalquilo C_{3-7} sustituido opcionalmente por $C(=O)-Z-R^{14}$, ftalimido-2-ilo, Het³ y $C(=O)Het^3$;

R^{12} y R^{13} son cada uno seleccionados independientemente a partir del hidrógeno, alquilo C_{1-4} , hidroxialquilo, dihidroxialquilo, fenilo, fenilalquilo, alquiloalquilo C_{1-4} , alquilcarbonilo C_{1-4} , fenilcarbonilo, mono- o di(alquilo C_{1-4})aminoalquilo C_{1-4} , fenilaminocarbonilo,

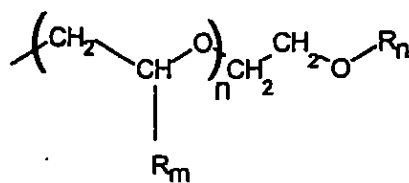
fenilaminotiocarbonilo, cicloalquilo C₃₋₇, piridinilC₁₋₄alquilo, alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-alcanediilo C₁₋₄-C(=O)-Z-R¹⁴ y R⁸; o R¹² y R¹⁵ tomados junto con el átomo de nitrógeno al cual se adhieren forman un radical de la siguiente formula:



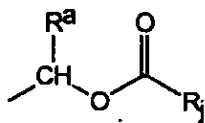
cada R¹⁴ representa independientemente hidrógeno, acilo C₁₋₂₀ (que tiene una cadena recta o bifurcada, saturada o insaturada de hidrocarbano que tiene de 1 a 20 átomos de carbono), alquilo C₁₋₂₀, alqueno C₃₋₂₀ sustituido opcionalmente por fenilo, alquino C₃₋₂₀, cicloalquilo C₃₋₇, polihaloalquiloC₁₋₂₀, Het⁵, fenilo o alquilo C₁₋₂₀ sustituido por uno o más sustitutos seleccionados a partir del hidroxil, NR¹⁷, R¹⁸, fenilo, mono- o di-(alquiloC₁₋₄)amino, ciano, Het⁵, alquiloxicarboniloC₁₋₄, fenilo alquiloxicarboniloC₁₋₄ y cicloalquiloC₃₋₇, o R¹⁴ representa un radical de la formula



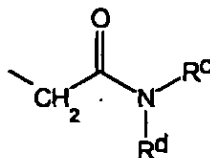
(a)



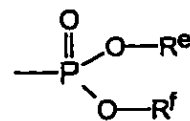
(b)



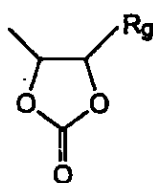
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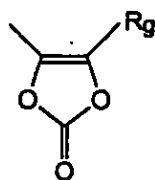
(d)



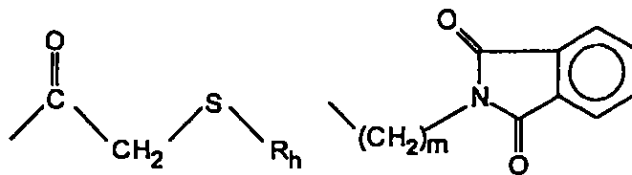
(e)



(h)

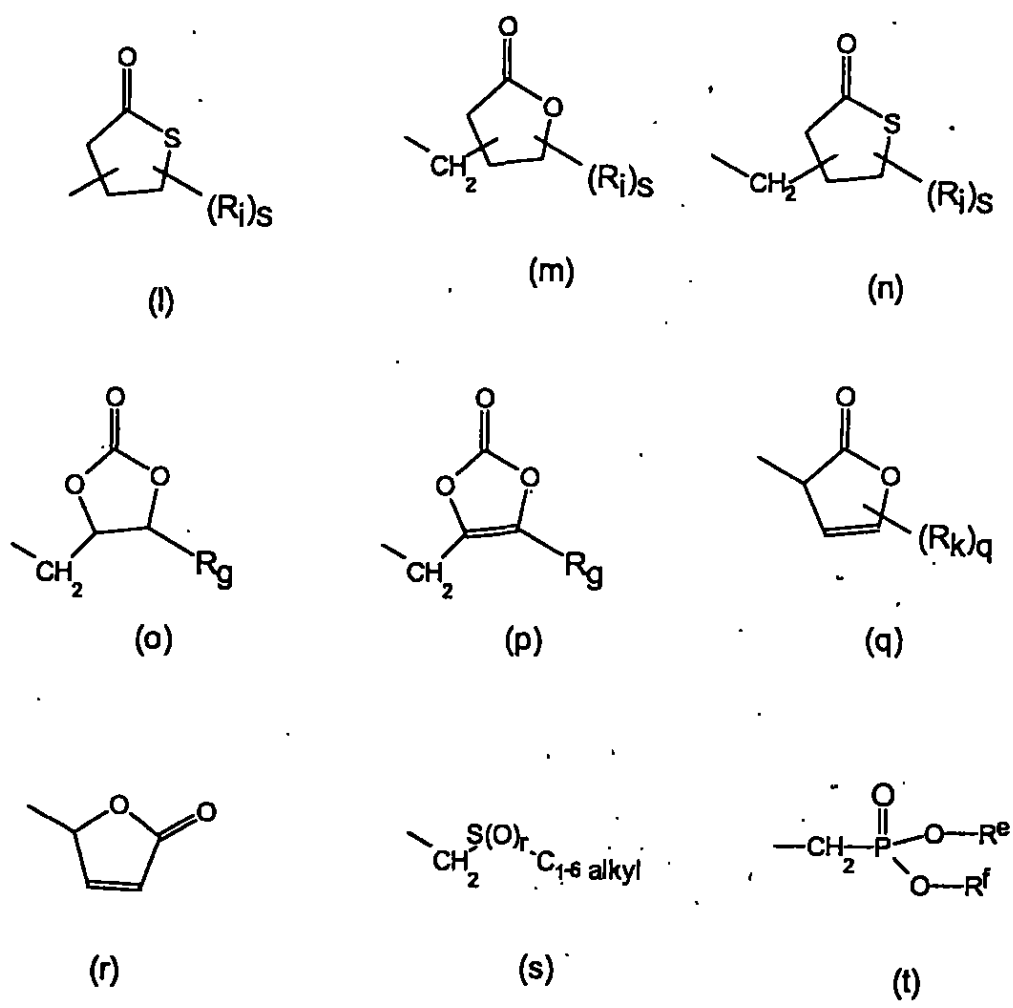


(i)



(j)

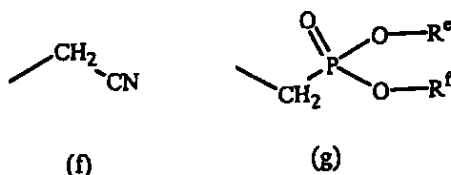
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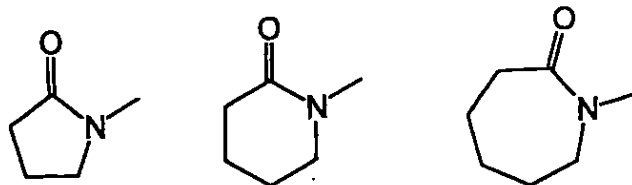
donde m es 1 a 4, n es 0 a 5, q es 0 a 2 y s es 0 a 4;
 R^a , R^b , R^c , R^d , R^e y R^f son cada una independientemente
 hidrógeno, alquilo C_{1-6} , fenilo o cicloalquilo C_3-7 ; o
 R^e y R^f tomados conjuntamente pueden formar $-CH_2-CH_2-$, $-$
 $CH_2-CH_2-CH_2-$, o $-CH_2-CH_2-CH_2-CH_2-$;
 R_m , R_n y R_k son cada uno independientemente hidrógeno o
 alquilo C_{1-4} ;
 R_i es alquilo C_{1-4} ;
 R_j es $-O-R_b$, alquilo C_{1-6} , fenilo o cicloalquilo C_3-7
 sustituido opcionalmente por alquilo C_{1-4} ;

donde R_m es hidrógeno o alquilo C_{1-4} y R_n es hidrógeno,
 alquilo C_{1-4} , cicloalquilo C_3-7 , fenilo o fenilalquilo C_{1-4}
 cada Z independientemente representa O, S, NH, $-CH_2-O-$ o $-$
 CH_2-S- donde $-CH_2-$ se adhiere al grupo carbonilo; o
 $-Z-R^{14}$ tomada conjuntamente forma un radical de la siguiente

formula



R^{15} y R^{16} son cada uno y de manera independiente seleccionados a partir del hidrógeno, alquilo C_1-4 , hidroxialquilo C_1-4 , dihidroxialquilo C_1-4 , arilo, arilo alquilo C_1-4 , alquilo C_1-4 alquilo C_1-4 , $-\text{C}(=\text{O})-\text{Z}-\text{R}^{14}$, arilcarbonilo, mono- o di(alquilo C_1-4)amino alquilo C_1-4 , arilaminocarbonilo, arilaminotiocarbonilo, aminocarbonilmetileno, mono- o di(alquilo C_1-4)aminocarbonilmetileno, Het^3 aminocarbonilo, Het^3 aminotiocarbonilo, piridinil alquilo C_1-4 , Het^3 , Het^4 o R^6 ; o R^{15} y R^{16} tomados junto con el átomo de nitrógeno al cual se adhieren forman un radical de la siguiente formula:



R^{17} y R^{18} son cada uno y de manera independiente seleccionados a partir del hidrógeno, alquilo C_1-4 , hidroxialquilo C_1-4 , dihidroxialquilo C_1-4 , fenilo, feniloalquilo C_1-4 , alquilo C_1-4 alquilo C_1-4 , alquilcarbonilo C_1-4 , fenilcarbonilo, mono- o di(alquilo C_1-4)amino alquilo C_1-4 , fenilaminocarbonilo, fenilaminotiocarbonilo, cicloalquilo C_3-7 , piridinilo alquilo C_1-4 , alcanediilo $\text{C}_1-4-\text{C}(=\text{O})-\text{Z}-\text{alquiloC}_1-8$, $-\text{C}(=\text{O})-\text{Z}-\text{alquiloC}_1-8$, $-\text{Y}-\text{alcanediiloC}_1-4-\text{C}(=\text{O})-\text{Z}-\text{alquiloC}_1-8$ y R^6 ;

arilo representa el fenilo sustituido opcionalmente por uno, dos o tres sustitutos cada uno de ellos seleccionados independientemente a partir del nitro, azido, ciano, halo, hidroxilo, alquilo C₁₋₄, cicloalquilo C₃₋₇, alquilo C₁₋₄, formilo, polihalo alquilo C₁₋₄, NR²R¹⁰, C(=O)NR²R¹⁰, C(=O)-Z-R¹⁴. R⁸, -O-R⁸, fenilo, Het³, C(=O)Het³ y alquilo C₁₋₄ sustituido por uno o más sustitutos donde cada uno de ellos se selecciona independientemente a partir del halo, hidroxilo, alquilo C₁₋₄, C(=O)-Z-R¹⁴, -Y-alcanediilo C₁₋₄-C(=O)-Z-R¹⁴, Het³ o NR²R¹⁰;

Het¹ representa un heterociclo seleccionado a partir del pirrolilo, pirrolinilo, imidazolilo, imidazolinilo, pirazolilo, pirazolinilo, triazolilo, tetrazolilo, furanilo, tetrahidrofuranilo, tienilo, tiolanilo, dioxolanilo, oxazolilo, oxazolinilo, isoxazolilo, tiazolilo, tiazolinilo, isotiazolilo, tiadiazolilo, oxadiazolilo, piridinilo, pirimidinilo, pirazinilo, piranilo, piridazinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, dioxanilo, ditianilo, tritiano, triazinilo, benzotienilo, isobenzotienilo, benzofuranilo, isobenzofuranilo, benzotiazolilo, benzoxazolilo, benzimidazolilo, indolilo, isoindolilo, indolinilo, purinilo, 1H-pirazolo[3,4-d] pirimidinilo, benzimidazolilo, quinolilo, isoquinolilo, cinnolinilo, ftalazinilo, quinazolinilo, guinoxalinilo, tiazolopiridinilo, oxazolopiridinilo e imidazo[2,1-b]-tiazolilo; donde los mencionados heterociclos cada uno de ellos y en forma independiente pueden sustituirse opcionalmente por uno, dentro de lo posible, dos o tres sustitutos cada uno seleccionados independientemente del Het², R¹¹ y alquilo C₁₋₄ sustituido opcionalmente por uno o

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dos sustitutos seleccionados independientemente del .Het² y R¹¹;

Het² representa un heterociclo seleccionado del pirrolilo, espirrolinilo, imidazolilo, imidazolinilo, pirazolilo, pirazolinilo, triazolilo, tetrazolilo, furanilo, tetrahidrofuranilo, tienilo, tiolanilo, dioxolanilo, oxazolilo, oxazolinilo, isoxazolilo, tiazolilo, tiazolinilo, iotiazolilo, tiadiazolilo, oxadiazolilo, piridinilo, pirimidinilo, pirazinilo, piranilo, piridazinilo, dioxanilo, ditianilo, tritianilo, triazinilo, benzotienilo, isobenzotienilo, benzofuranilo, isobenzofuranilo, benzotiazolilo, benzoxazolilo, indolilo, isoindolilo, indolinilo, purinilo, 1H-pirazolo[3,4-d] pirimidinilo, benzimidazolilo, quinolilo, isoquinolilo, cinnolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, tiazolopiridinilo, oxazolopiridinilo e imidazo[2,1-b]-tiazolilo; donde los mencionados heterociclos cada uno de ellos y en forma independiente pueden sustituirse opcionalmente por uno, dentro de lo posible, dos o tres sustitutos cada uno seleccionados independientemente del Het⁴, R¹¹ y alquilo C₁₋₄ sustituido opcionalmente por uno o dos sustitutos seleccionados independientemente del Het⁴ y R¹¹;

Het³ representa un heterociclo monocíclico seleccionado del pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo y tetrahidropiranilo; donde los heterociclos monicíclicos mencionados cada uno de ellos independientemente pueden ser opcionalmente sustituidos por uno, dos, tres o cuatro posibles sustitutos, cada uno de ellos seleccionados independientemente del hidroxí, alquilo C₁₋₄, alquiloxi C₁₋₄,

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alquilcarboniloC₁₋₄, piperidinilo, NR¹²R¹³, C(=O)-Z-R¹⁴, R⁸ y alquiloC₁₋₄ sustituido por uno o dos sustitutos seleccionados independientemente del hidroxilo, alquiloC₁₋₄, fenilo, C(=O)-Z-R¹⁴, -Y-alcanediiloC₁₋₄-C(=O)-Z-R¹⁴, R⁸ y NR¹²R¹³;

Het⁴ representa un heterociclo monocíclico seleccionado del pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, furanilo, tienilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, tiadiazolilo, oxadiazolilo, piridinilo, pirimidinilo, pirazinilo, pirazinilo, piranilo, piridazinilo y triazinilo;

Het⁵ representa un heterociclo seleccionado a partir del pirrolilo, pirrolinilo, imidazolilo, imidazolinilo, pirazolilo, pirazolinilo, triazolilo, tetrazolilo, furanilo, tetrahidrofuranilo, tienilo, tiolanilo, dioxolanilo, oxazolilo, oxazolinilo, isoxazolilo, tiazolilo, tiazolinilo, isotiazolilo, tiadiazolilo, oxadiazolilo, piridinilo, pirimidinilo, pirazinilo, piranilo, piridazinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tetrahidropiranilo, dioxanilo, ditianilo, tritiano, triazinilo, benzotienilo, isobenzotienilo, benzofuranilo, isobenzofuranilo, benzotiazolilo, benzoxazolilo, benzodioxanilo, indolilo, isoindolilo, indolinilo, purinilo, 1H-pirazolo[3,4-d]pirimidinilo, benzimidazolilo, quinolilo, isoquinolilo, cinnolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, tiazolopiridinilo, oxazolopiridinilo y imidaz[2,1-b]tiazolilo; donde los heterociclos monocíclicos mencionados cada uno de ellos independientemente pueden ser opcionalmente sustituidos por uno, dos, tres o cuatro posibles sustitutos, cada uno de

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ellos seleccionados independientemente del hidroxil, alquilo C₁₋₄, alquilo C₁₋₄, alquilcarboniloC₁₋₄, piperidinilo, NR¹⁷R¹⁸, C(=O)-Z-alquiloC₁₋₈, R⁸, sulfonamido y alquiloC₁₋₄ sustituido por uno o dos sustitutos seleccionados independientemente del hidroxil, alquiloC₁₋₄, fenilo, C(=O)-Z-alquiloC₁₋₈, -Y-alcanediiloC₁₋₄-C(=O)-Z-alquiloC₁₋₈, R⁸ y NR¹⁷R¹⁸;

a condición de que:

- R² sea distinto del alquiloxicarboniloC₁₋₈-alquiloC₁₋₈, aminocarbonilo; y
- R⁷, R⁸, R⁹ y R¹⁰ sean distintos del aminocarbonilo, alquilcarboniloxiC₁₋₄-alquilcarboniloC₁₋₄, hidroxil alquilcarboniloC₁₋₄, alquiloxicarbonilcarboniloC₁₋₄ C(=O)-O-R¹⁹, alcanediiloC₁₋₄C(=O)-O-R¹⁹ o -Y-alcanediiloC₁₋₄C(=O)-O-R¹⁹; y
- R¹² y R¹³ sean distintos del alquilcarboniloxiC₁₋₄-alquilcarboniloC₁₋₄, hidroxil alquilcarboniloC₁₋₄, o alquilcarbonilcarboniloC₁₋₄; y
- R¹¹ es distinto de C(=O)-O-R¹⁹, Y-alcanediiloC₁₋₄ - C(=O)-OR¹⁹, C(=O)NH₂, C(=O)NHalquiloC₁₋₄ o C(=O)NHcicloalquiloC₃₋₇; y
- R¹⁵ y R¹⁶ son distintos del aminocarbonilo, alquilcarboniloxiC₁₋₄-alquilcarboniloC₁₋₄, hidroxil alquilcarboniloC₁₋₄ o alquiloxicarbonilcarboniloC₁₋₄; y
- Arilo es distinto del fenilo sustituido por C(=O)-O-R¹⁹ C(=O)NH₂, C(=O)NHalquiloC₁₋₄, C(=O)NHcicloalquiloC₃₋₇ y/o por alquiloC₁₋₄ sustituido por C(=O)-O-R¹⁹ o Y-alcanediiloC₁₋₄ - C(=O)-O-R¹⁴; y
- Het³ es distinto del heterociclo monocíclico sustituido por C(=O)-O-R¹⁹ y/o por alquiloC₁₋₄ sustituido por

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- $C(=O)-O-R^{1a}$ y/o Y -alcanediilo $C_{1-4} - (C(=O)-O-R^{1a})$; y
- en cada una de las condiciones anteriores R^{1a} se define como hidrógeno, alquilo C_{1-4} , cicloalquilo C_{3-7} , aminocarbonilmetileno o mono- o di(alquilo C_{1-4})aminocarbonilmetileno; y
 - El compuesto mencionado de la formula (I) contiene por lo menos un medio $-C(=O)-Z-R^{14}$.

2. Un compuesto según se describe en la reivindicación 1 donde la porción 6-azauracilo se encuentra en una posición relativa al átomo de carbono que lleva los sustitutos $-X-R^2$, R^3 y R^4 .

3. Un compuesto según se describió en las reivindicaciones 1 o 2 donde R^2 es un heterociclo monocíclico seleccionado a partir de pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, furanilo, tienilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, tiadiazolilo, oxadiazolilo, piridinilo, pirimidinilo, pirazinilo, piranilo, piridazinilo y triazinilo, donde los mencionados heterociclos monocíclicos pueden cada uno independientemente y en forma opcional sustituirse por uno, o si es posible dos o tres sustitutos cada uno de ellos seleccionados independientemente del Het^2 , R^{11} y alquilo C_{1-4} sustituido opcionalmente por Het^2 o R^{11} .

4. Un compuesto según se describió en una de las reivindicaciones 1 a 3 donde R^3 y R^4 son ambos metilo y $-X-R^2$ es Het^1 .


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5. Un compuesto según se describió en una de las reivindicaciones 1 a 4 donde p es 1 o 2 y cada R¹ es cloro.

6. Un compuesto que comprende un portador farmacéuticamente aceptable y como ingrediente activo una cantidad terapéuticamente eficaz de un compuesto según se reivindica en una de las reivindicaciones 1 a 5.

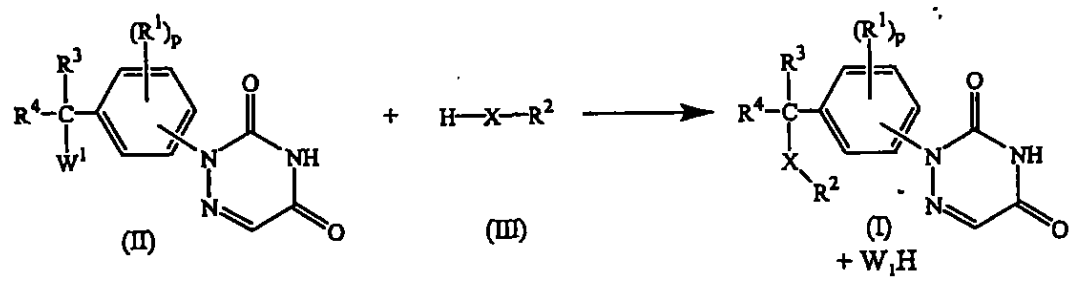
7. Un proceso para la preparación de un compuesto según se reivindica en la reivindicación 6, donde un portador farmacéuticamente aceptable se mezcla íntimamente con una cantidad terapéuticamente eficaz de un compuesto según se define en una de las reivindicaciones 1 a 5.

8. Un compuesto según se define en una de las reivindicaciones 1 a 5 para utilizarse como medicamento.

9. La utilización de un compuesto según se define en una de las reivindicaciones 1 a 5 para la elaboración de un medicamento para el tratamiento de enfermedades inflamatorias eosinófilo-dependientes.

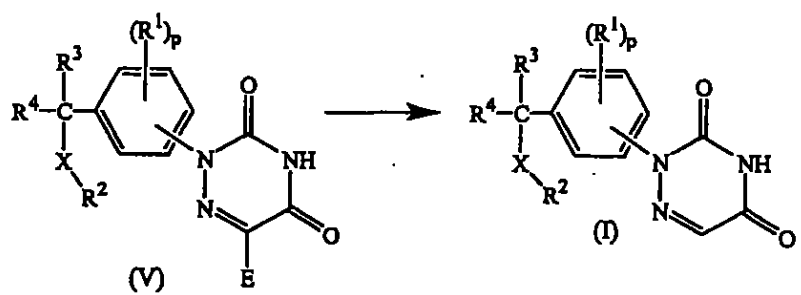
10. Un proceso para la preparación de un compuesto según se define en la reivindicación 1, que comprende el paso de:

(a) la reacción de un intermedio de la formula (II) donde W¹ es un grupo adecuado saliente que tiene un reactivo apropiado de la formula (III) opcionalmente en un solvente inerte a la reacción y opcionalmente en presencia de una base a una temperatura entre -70°C y la temperatura de reflujo;



donde R¹, R², R³, R⁴, p y X corresponden a la definición dada en la reivindicación 1 o;

b) eliminación del grupo E de una triazinediona de la formula (V)



donde E es un electrón apropiado que atrae al grupo y R¹, R², R³, R⁴, X y p corresponden a la definición dada en la reivindicación 1; y

si se desea se transforman los compuestos de la formula (I) en cada una de las siguientes transformaciones conocidas en la técnica y posteriormente si se desea se transforman los compuestos de la formula (I), en una sal de adición ácida no tóxica terapéuticamente activa por tratamiento con un ácido, o en una sal de adición base no tóxica terapéuticamente activa por tratamiento con una base, o inversamente, la transformación de la forma de la sal de adición ácida en la base libre por medio del tratamiento con alcali, o la transformación de la sal de adición de base en el ácido libre

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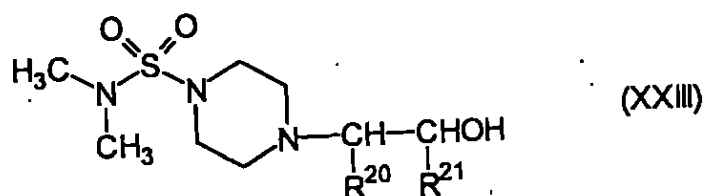
por tratamiento con ácido; y además si se desea, la preparación de las formas estereoquímicamente isoméricas de sus formas N-óxido.

11. Un proceso de marcación de un receptor que comprende los siguientes pasos:

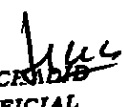
- a) radioetiquetado de un compuesto según se define en la reivindicación 1;
- b) administración de dicho compuesto radioetiquetado al material biológico,
- c) detección de las emisiones provenientes del compuesto radioetiquetado.

12. Un proceso de imagen de un órgano, caracterizado por, la administración de una cantidad suficiente de un compuesto radioetiquetado de la fórmula (I) en una composición apropiada, y la detección de las emisiones provenientes del compuesto radioactivo.

13. Un compuesto de la fórmula:



donde R^{20} y R^{21} se seleccionan cada uno independientemente del hidrógeno o alquilo C_{1-20} , o R^{20} y R^{21} tomados conjuntamente con el átomo de carbono al cual se adhieren forman un radical cicloalquilo.


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14. La utilización del compuesto de la reivindicación 13 para preparar un compuesto de la reivindicación 1 donde Het⁵ representa una piperazina sustituida de sulfonamido.

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Santafé de Bogotá D.C., Septiembre 4 del 2000.

Luc
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MINISTERIO DE JUSTICIA



Europäisches
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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99126035.7

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 23/08/00
LA HAYE, LE

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Demande n°:

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Date of filing: 27/12/99
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
JANSSEN PHARMACEUTICA N.V.
2340 Beerse
BELGIUM

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:

Non-steroidal IL-5 inhibitors, processes for their preparation and pharmaceutical compositions comprising them

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

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State:
Pays:

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Date:
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Numéro de dépôt:

EPA 99870170

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:

/

Am Anmeldetag benannte Vertragsstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:

27. Dez. 1999

**NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM**

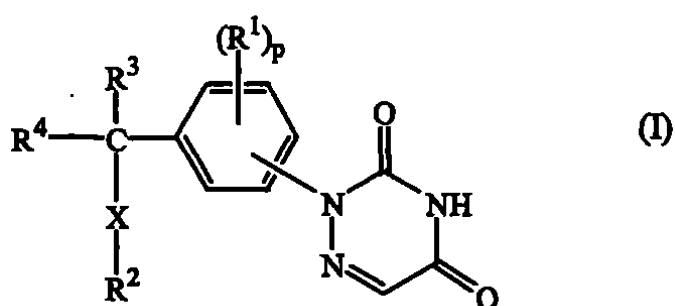
5 The present invention concerns IL-5 inhibiting 6-azauracil derivatives useful for treating eosinophil-dependent inflammatory diseases; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

10 Eosinophil influx, leading to subsequent tissue damage, is an important pathogenic event in bronchial asthma and allergic diseases. The cytokine interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces the differentiation of eosinophils in bone marrow and, primes eosinophils for activation in peripheral blood and sustains their survival in tissues. As such, IL-5 plays a critical role in the process of eosinophilic inflammation. Hence, the possibility that inhibitors of IL-5 production
15 therapeutic approach to the treatment of bronchial asthma and allergic diseases such as, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent inflammatory diseases.

20 Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as the only drugs with remarkable efficacy for bronchial asthma and atopic dermatitis, but they cause various serious adverse reactions such as diabetes, hypertension and cataracts. Therefore, it would be desirable to find non-steroidal compounds having the ability to inhibit IL-5 production in human T-cells and which have little or no adverse reactions.

25 US 4,631,278 discloses α -aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-benzeneacetonitriles and US 4,767,760 discloses 2-(substituted phenyl)-1,2,4-triazine-3,5(2H,4H)-diones, all having anti-protozoal activity, in particular, anti-coccidial activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones as anticoccidial agents. WO99/02505 discloses 6-azauracil derivatives which prove to be potent inhibitors of
30 the production of IL-5.

The present invention is concerned with the compounds of formula



the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

5 *p* represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR⁵ or a direct bond or *X*-R² taken together may represent cyano;

Y represents O, S, NR⁵, or S(O)₂;

each R¹ independently represents C(=O)-Z-R¹⁴, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl,

hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano,
10 nitro, Het³, R⁶, NR⁷R⁸ or C₁₋₄alkyl substituted with C(=O)-Z-R¹⁴, Het³, R⁶ or NR⁷R⁸;

R² represents Het¹, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkyl or
C₁₋₆alkyl substituted with one or two substituents selected from C(=O)-Z-R¹⁴,

hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy optionally
substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylsulfonyloxy, C₃₋₇cycloalkyl optionally
15 substituted with C(=O)-Z-R¹⁴, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and
if *X* is O, S or NR⁵, then R² may also represent aminothiocabonyl, C₁₋₄alkylcarbonyl
optionally substituted with C(=O)-Z-R¹⁴, C₁₋₄alkylthiocarbonyl optionally substituted
with C(=O)-Z-R¹⁴, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl;

R³ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl;

20 R⁴ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; or

R³ and R⁴ taken together form a C₂₋₆alkanediyl;

R⁵ represents hydrogen or C₁₋₄alkyl;

each R⁶ independently represents C₁₋₆alkylsulfonyl, aminosulfonyl, piperidinylsulfonyl,

mono- or di(C₁₋₄alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl,
25 polyhaloC₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl, phenylC₁₋₄alkylsulfonyl,
piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl,

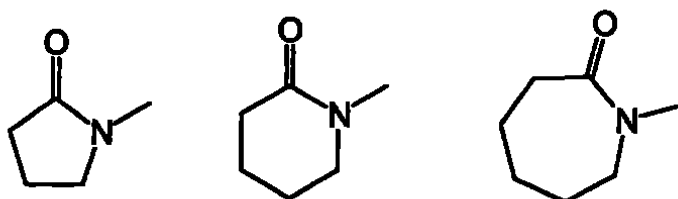
N-C₁₋₄alkyl-*N*-piperidinylaminosulfonyl or mono-or

di(C₁₋₄alkyl)aminoC₁₋₄alkylsulfonyl;

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each R^7 and each R^8 are independently selected from hydrogen, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, arylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl,

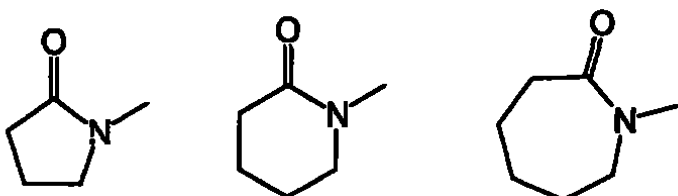
- 5 Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³, Het⁴ and R^6 ; or R^7 and R^8 taken together with the nitrogen atom to which they are attached form a radical of formula



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R^9 and R^{10} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl,

- 15 Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³, Het⁴ and R^6 ; or R^9 and R^{10} taken together with the nitrogen atom to which they are attached form a radical of formula

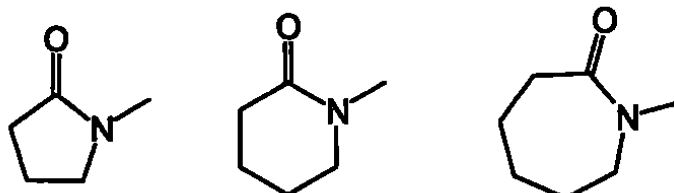


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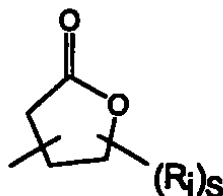
each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4} alkyloxy optionally substituted with C(=O)-Z- R^{14} , formyl, trihalo C_{1-4} alkylsulfonyloxy, R^6 , NR^7R^8 , C(=O) $NR^{15}R^{16}$, -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , aryl, aryloxy, arylcarbonyl, C_{3-7} cycloalkyl optionally substituted with C(=O)-Z- R^{14} , C_{3-7} cycloalkyloxy optionally substituted with C(=O)- R^{14} , phthalimide-2-yl, Het³ and C(=O)Het³;

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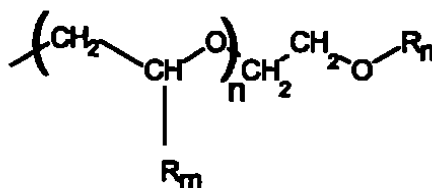
- R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} and R^6 ; or R^{12} and R^{13} taken together with the nitrogen atom to which they are attached form a radical of formula



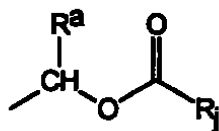
- each R^{14} independently represents hydrogen, C_{1-20} acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C_{1-20} alkyl, C_{3-20} alkenyl optionally substituted with phenyl, C_{3-20} alkynyl, C_{3-7} cycloalkyl, polyhalo C_{1-20} alkyl, Het⁵, phenyl or C_{1-20} alkyl substituted with one or more substituents selected from hydroxy, $NR^{17}R^{18}$, phenyl, mono- or di-(C_{1-4} alkyl)amino, cyano, Het⁵, C_{1-4} alkyloxycarbonyl, phenyl C_{1-4} alkyloxycarbonyl and C_{3-7} cycloalkyl, or R^{14} represents a radical of formula



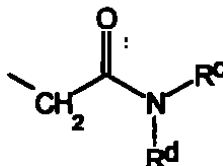
(a)



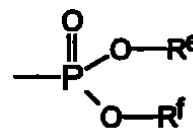
(b)



(c)

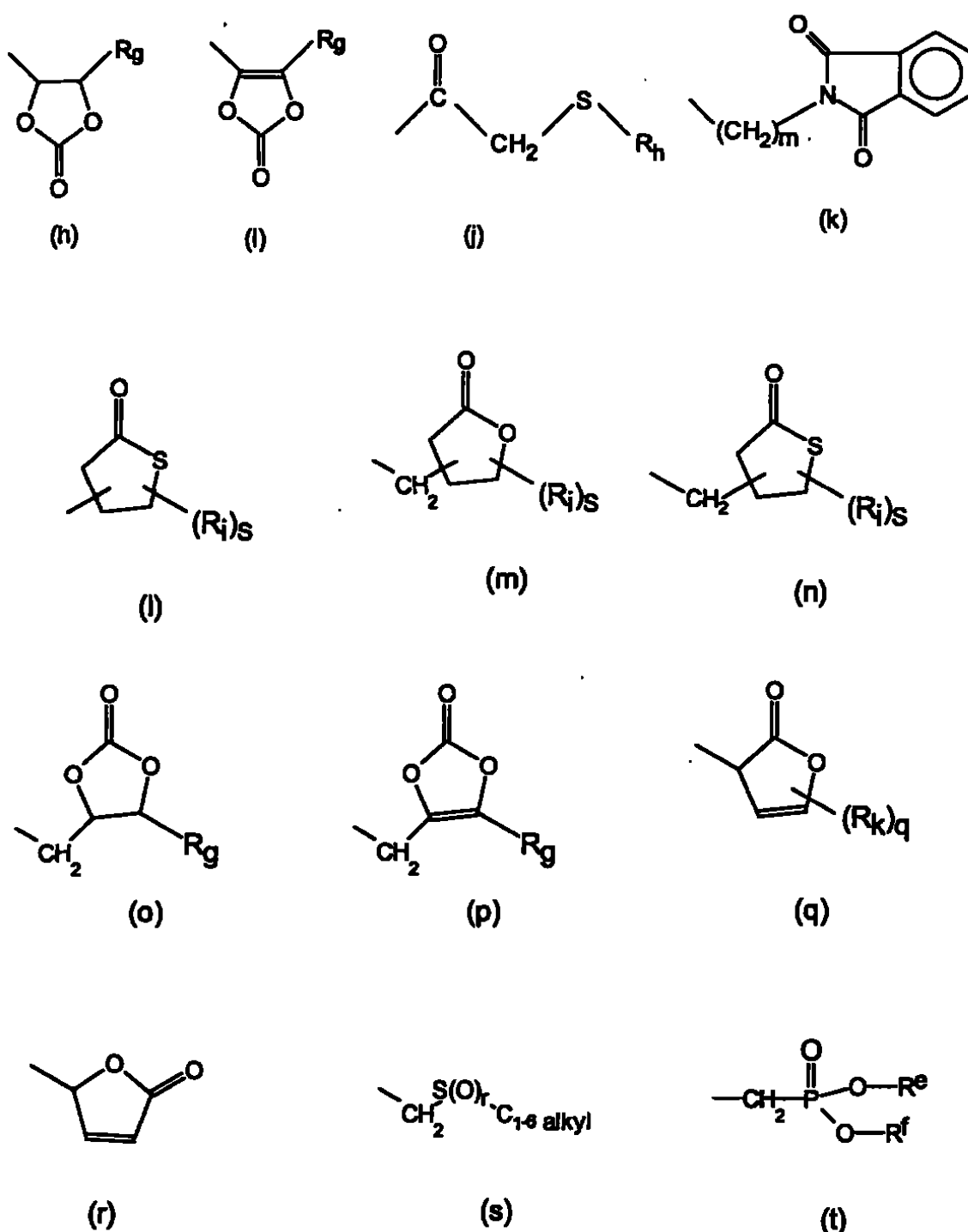


(d)



(e)

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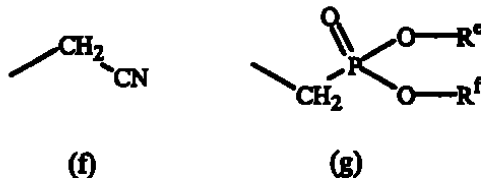


- 5 wherein m is 1 to 4, n is 0 to 5, q is 0 to 2, r is 0 to 2 and s is 0 to 4;
 R^a , R^b , R^c , R^d , R^e and R^f are each independently hydrogen, C_{1-8} alkyl, phenyl or C_{3-7} cycloalkyl; or
 R^e and R^f taken together may form $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-CH_2-$;
10 R_p , R_k and R_x are each independently hydrogen or C_{1-4} alkyl
 R_i is C_{1-4} alkyl;

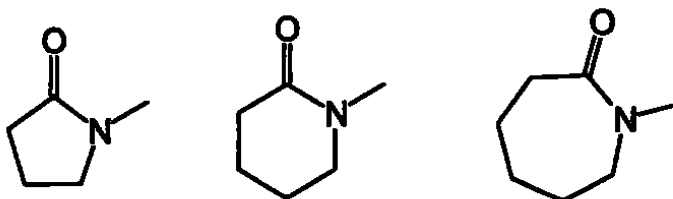
R_j is $-O-R_b$, C_{1-6} alkyl, phenyl or C_{3-7} cycloalkyl optionally substituted with C_{1-4} alkyloxy;

where R_m is hydrogen or C_{1-4} alkyloxy and R_n is hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, phenyl or phenyl C_{1-4} alkyl

- 5 each Z independently represents O, S, NH, $-CH_2-O-$ or $-CH_2-S-$ whereby $-CH_2-$ is attached to the carbonyl group; or
 $-Z-R^{14}$ taken together form a radical of formula



- R^{15} and R^{16} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl,
 10 dihydroxy C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, $-C(=O)-Z-R^{14}$,
 arylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, arylaminocarbonyl,
 arylaminothiocarbonyl, aminocarbonylmethylene, mono- or di(C_{1-4} alkyl)
 aminocarbonylmethylene, Het³aminocarbonyl, Het³aminothiocarbonyl,
 pyridinyl C_{1-4} alkyl, Het³ or R^6 ; or R^{15} and R^{16} taken together with the nitrogen atom to
 15 which they are attached form a radical of formula



- R^{17} and R^{18} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl,
 dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl,
 phenylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl,
 20 phenylaminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl- $C(=O)-$
 $Z-C_{1-6}$ alkyl, $-C(=O)-Z-C_{1-6}$ alkyl, $-Y-C_{1-4}$ alkanediyl- $C(=O)-Z-C_{1-6}$ alkyl and R^6 ;
 aryl represents phenyl optionally substituted with one, two or three substituents each
 independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4} alkyl, C_{3-7} cyclo-
 alkyl, C_{1-4} alkyloxy, formyl, polyhalo C_{1-4} alkyl, NR^9R^{10} , $C(=O)NR^9R^{10}$, $C(=O)-Z-$
 25 R^{14} , R^6 , $-O-R^6$, phenyl, Het³, $C(=O)Het^3$ and C_{1-4} alkyl substituted with one or more
 substituents each independently selected from halo, hydroxy, C_{1-4} alkyloxy, $C(=O)-Z-$
 R^{14} , $-Y-C_{1-4}$ alkanediyl- $C(=O)-Z-R^{14}$, Het³ or NR^9R^{10} ;

Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolanyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het² and R¹¹;

Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolanyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het⁴, R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het⁴ and R¹¹;

Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹²R¹³, C(=O)-Z-R¹⁴, R⁶ and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, phenyl, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, R⁶ and NR¹²R¹³;

Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl;

- 5 Het⁵ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-
- 10 d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-
- 15 b]thiazolyl; wherein said heterocycles each independently may be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹⁷R¹⁸, C(=O)-Z-C₁₋₆alkyl, R⁶, sulfonamido and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, phenyl, C(=O)-Z-C₁₋₆alkyl,
- 20 -Y-C₁₋₄alkanediyl-C(=O)-Z-C₁₋₆alkyl, R⁶ and NR¹⁷R¹⁸;

provided however that

- R² is other than C₁₋₆ alkyloxycarbonylC₁₋₆alkyl or aminocarbonyl; and
- R⁷, R⁸, R⁹ and R¹⁰ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, C(=O)-O-R¹⁹, C₁₋₄alkanediylC(=O)-O-R¹⁹ or -Y-C₁₋₄alkanediylC(=O)-O-R¹⁹; and
- R¹² and R¹³ are other than C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl or C₁₋₄alkylcarbonylcarbonyl; and
- R¹¹ is other than C(=O)-O-R¹⁹, Y-C₁₋₄alkanediyl - C(=O)-OR¹⁹, C(=O)NH₂, C(=O)NHC₁₋₄alkyl or C(=O)NHC₃₋₇cycloalkyl; and
- 30 • R¹⁵ and R¹⁶ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl or C₁₋₄alkyloxycarbonylcarbonyl; and
- aryl is other than phenyl substituted with C(=O)-O-R¹⁹, C(=O)NH₂, C(=O)NHC₁₋₄alkyl, C(=O)NHC₃₋₇cycloalkyl and/or with C₁₋₄alkyl substituted with

6.2.77

$C(=O)-O-R^{19}$ or $Y-C_{1-4}alkanediyl - C(=O)-O-R^{14}$; and

- Het^3 is other than a monocyclic heterocycle substituted with $C(=O)-O-R^{19}$ and/or with $C_{1-4}alkyl$ substituted with $C(=O)-O-R^{19}$ and/or $Y-C_{1-4}alkanediyl - C(=O)-O-R^{19}$; and
- 5 • in each of the above proviso's R^{19} is defined as hydrogen, $C_{1-4}alkyl$, $C_{3-7}cycloalkyl$, aminocarbonylmethylene or mono- or di($C_{1-4}alkyl$)aminocarbonylmethylene; and the said compound of formula (I) contains at least one $-C(=O)-Z-R^{14}$ moiety.

- As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; $C_{3-7}cycloalkyl$ is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; $C_{1-4}alkyl$ defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; $C_{1-6}alkyl$ is meant to include $C_{1-4}alkyl$ and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; $C_{1-20}alkyl$ is meant to include $C_{1-6}alkyl$ and the higher homologues thereof having 7 to 20 carbon atoms such as, for example, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl, nonadecyl, eicosyl and the like; $C_{3-20}alkyl$ is meant to include $C_{1-20}alkyl$ except for $C_{1-4}alkyl$; $C_{3-20}alkenyl$ defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 20 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-hexenyl and the like, the carbon atom of the said $C_{3-20}alkenyl$ connected to the remainder of the molecule being preferably saturated; $C_{3-20}alkynyl$ defines straight and branched chain hydrocarbon radicals containing one triple bond and having from 3 to 20 carbon atoms such as, for example, 2-propynyl, 3-butynyl, 2-butynyl, 2-pentynyl, 3-pentynyl, 3-methyl-2-butynyl, 3-hexynyl and the like, the carbon atom of the said $C_{3-20}alkynyl$ connected to the remainder of the molecule being preferably saturated; polyhalo $C_{1-4}alkyl$ is defined as polyhalosubstituted $C_{1-4}alkyl$, in particular $C_{1-4}alkyl$ substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhalo $C_{1-6}alkyl$ is defined as polyhalosubstituted $C_{1-6}alkyl$; polyhalo $C_{1-20}alkyl$ is defined as polyhalosubstituted $C_{1-20}alkyl$. The term $C_{1-4}alkanediyl$ defines bivalent straight or branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl

and the like; C_{2-6} alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 2 to 6 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like.

- 5 Het¹, Het², Het³, Het⁴ and Het⁵ are meant to include all possible isomeric forms of the heterocycles mentioned in the above definitions, for instance pyrrolyl also includes 2*H*-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-
10 thiadiazolyl; pyranlyl includes 2*H*-pyranlyl and 4*H*-pyranlyl.

- The heterocycles represented by Het¹, Het², Het³, Het⁴ and Het⁵ may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a
15 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it is benzothiazolyl, it may be 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl and 7-benzothiazolyl.

20

The C_{1-20} acyl is derived from

acetic acid	CH ₃ COOH	tridecanoic acid	C ₁₂ H ₂₅ COOH
propionic acid	C ₂ H ₅ COOH	myristic acid	C ₁₃ H ₂₇ COOH
butyric acid	C ₃ H ₇ COOH	pentadecanoic acid	C ₁₄ H ₂₉ COOH
valeric acid	C ₄ H ₉ COOH	palmitic acid	C ₁₅ H ₃₁ COOH
hexanoic acid	C ₅ H ₁₁ COOH	heptadecanoic acid	C ₁₆ H ₃₃ COOH
heptanoic acid	C ₆ H ₁₃ COOH	stearic acid	C ₁₇ H ₃₅ COOH
octanoic acid	C ₇ H ₁₅ COOH	oleic acid	C ₁₇ H ₃₃ COOH
nonanoic acid	C ₈ H ₁₇ COOH	linolic acid	C ₁₇ H ₃₁ COOH
decanoic acid	C ₉ H ₁₉ COOH	linolenic acid	C ₁₇ H ₂₉ COOH
undecanoic acid	C ₁₀ H ₂₁ COOH	nonadecanoic acid	C ₁₈ H ₃₇ COOH
lauric acid	C ₁₁ H ₂₃ COOH	icosanoic acid	C ₁₉ H ₃₉ COOH

- The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by
- 5 treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic,
- 10 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.
- 15 The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g.
- 20 the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form. The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g.
- 25 hydrates, alcoholates and the like.

- The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide. For example, one or more nitrogen atoms of any of the heterocycles in the definition of
- 30 Het¹, Het², Het³, Het⁴ and Het⁵ may be *N*-oxidized.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included

within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

- 5 The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular,
- 10 stereogenic centers may have the R- or S-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

- The compounds of formula (I) and some of the intermediates in the present invention
- 15 contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the present invention.

- Whenever used hereinafter, the term "compounds of formula (I)" is meant to also
- 20 include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

- An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative
- 25 to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents; preferably in the para position. Another interesting group contains those compounds of formula (I) wherein one or more of the following restrictions apply :

- p is 0, 1 or 2;
- X is S, NR^5 or a direct bond; more preferably a direct bond;
- 30 • each R^1 independently is halo, polyhalo C_{1-6} alkyl, C_{1-6} alkyl, C_{1-6} alkyloxy or aryl, preferably, chloro or trifluoromethyl, more preferably chloro;
- the at least one $-C(=O)-Z-R^{14}$ moiety contained by the compound of formula (I) is born by R^2 ,

- R^2 is Het¹ or C₁₋₆alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C(=O)-Z-R¹⁴, C₁₋₆alkyloxy optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylsulfonyloxy, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if
5 X is O, S or NR⁵, then R^2 may also represent aminothiocarbonyl, C₁₋₄alkylcarbonyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₄alkylthiocarbonyl optionally substituted with C(=O)-Z-R¹⁴, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; more preferably R^2 is Het¹;
- R^3 is hydrogen, methyl, ethyl, propyl or cyclohexyl, more preferably methyl;
- 10 • R^4 is hydrogen or methyl, more preferably methyl;
- R^3 and R^4 are taken together to form a 1,4-butanediyl;
- R^6 is C₁₋₆alkylsulfonyl or aminosulfonyl;
- R^7 and R^8 are each independently hydrogen, C₁₋₄alkyl, Het³ or R⁶;
- R^9 and R^{10} are each independently hydrogen, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl,
15 aminocarbonyl, Het³carbonyl, Het³ or R⁶;
- R^{11} is cyano, nitro, halo, C₁₋₄alkyloxy, formyl, NR⁷R⁸, C(=O)NR¹⁵R¹⁶, -C(=O)-Z-R¹⁴, aryl, arylcarbonyl, Het³ or C(=O)Het³; more preferably R^{11} is phenyl, -C(=O)-O-R¹⁴, -C(=O)-S-R¹⁴ or -C(=O)-NH-R¹⁴.
- R^{14} is dihydrofuranyl, C₅₋₂₀alkyl, C₃₋₂₀alkenyl, polyhaloC₁₋₆alkyl, Het⁵ or C₁₋₂₀alkyl
20 substituted with one or more substituents selected from phenyl, C₁₋₄alkylamino, cyano, Het¹, hydroxy and C₃₋₇cycloalkyl;
- R^{17} and R^{18} are each independently hydrogen or phenyl;
- aryl is phenyl optionally substituted with one, two or three substituents each independently selected from nitro, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cycloalkyl,
25 C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-O-R¹⁴, -O-R⁶, phenyl, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, Het³ and NR⁹R¹⁰;
- Het¹ is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl,
30 triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted

- with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹; more preferably Het¹ is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹;
- 5 ♦ Het² is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl or benzothienyl, wherein said aromatic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R¹¹ and C₁₋₄alkyl;
- 10 ♦ Het³ is piperidinyl, piperazinyl, morpholinyl or tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkylcarbonyl, piperidinyl and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy and phenyl;
- 15 ♦ Het⁴ is thienyl;
- ♦ Het⁵ is piperidinyl or piperazinyl optionally substituted with C₁₋₄alkyl or sulfonamido.

Special compounds are those compounds of formula (I) wherein p is 2 and both R¹ substituents are chloro; more preferably the two chloro substituents are in the ortho positions relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

20

Particular compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

25

Other particular compounds are those compounds of formula (I) wherein X is a direct bond and R² is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranal, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted

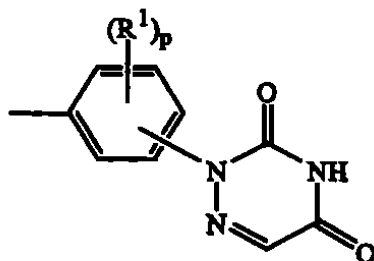
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with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹; more in particular R² is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

- 5 Preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are both methyl and -X-R² is Het¹ wherein Het¹ suitably is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

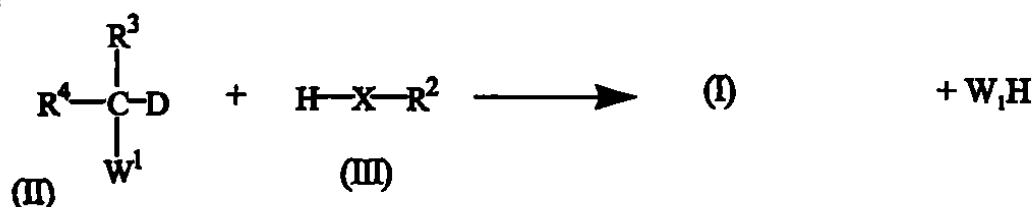
- 10 More preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are both methyl, -X-R² is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

- 15 In order to simplify the structural representation of the compounds of formula (I), the group



will hereinafter be represented by the symbol D.

- 20 Compounds of formula (I) can generally be prepared by a series of reactions comprising the step of reacting an intermediate of formula (II) wherein W¹ is a suitable leaving group such as, for example, a halogen atom, with an appropriate reagent of formula (III).



- 25 Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no

additional reaction-inert solvent is required. The reaction is optionally carried out in the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium bicarbonate, sodiummethanolate and the like. Convenient reaction temperatures range between -70°C and reflux temperature.

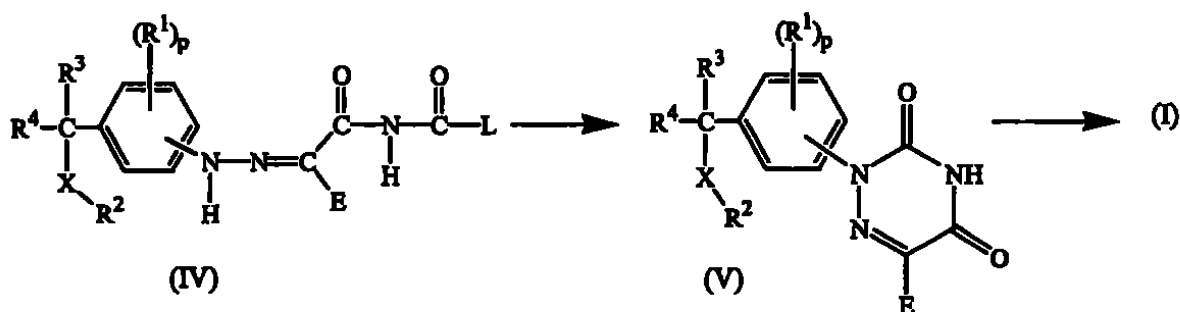
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In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

10

Some of the compounds and intermediates of the present invention can be prepared according to or analogous to the procedures described in EP-A-0,170,316, EP-A-0,232,932 and WO99/02505.

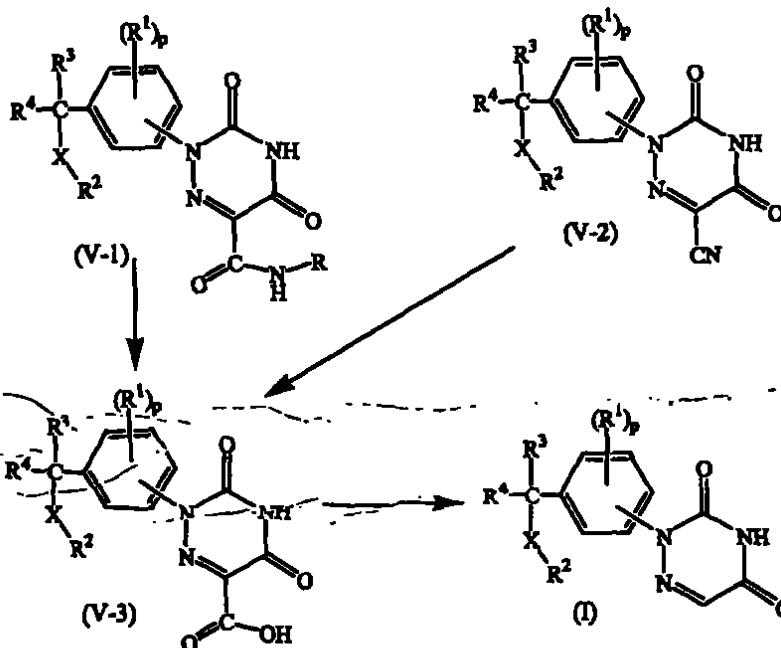
- 15 Alternatively, for instance, compounds of formula (I) may generally be prepared by cyclizing an intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C₁₋₆alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide, a cyanide, C₁₋₆alkylsulfonyloxy and the like groups; and eliminating the group E of the thus obtained triazinedione of formula
- 20 (V). The cyclization can suitably be carried out by refluxing the intermediate (IV) in acidic medium such as acetic acid and in the presence of a base such as, for example, potassium acetate.



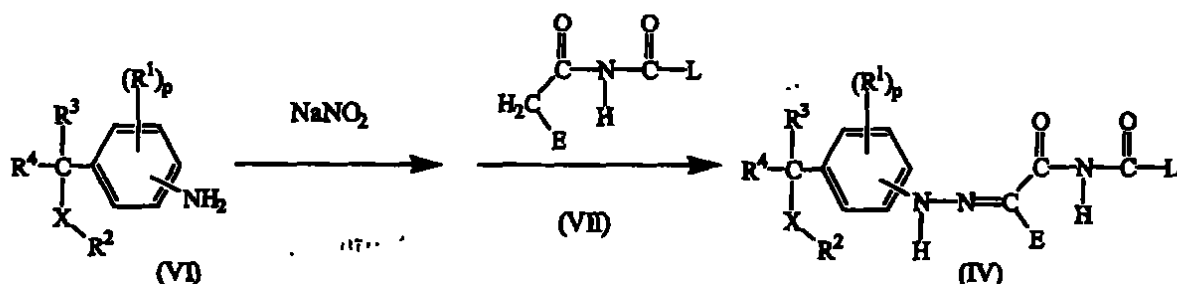
- Depending on its nature, E can be eliminated using various art-known elimination
- 25 procedures. For example when E is an amide or a cyano moiety, it can be hydrolyzed to a carboxylic moiety by for instance refluxing the intermediate bearing the E group in hydrochloric acid and acetic acid. The thus obtained intermediate can then be further reacted with mercaptoacetic acid or a functional derivative thereof to obtain a compound of formula (I). Said reaction is conveniently carried out at elevated

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temperatures ranging up to reflux temperature.



A suitable way to prepare intermediates of formula (IV) involves the reaction of an intermediate of formula (VI) with sodium nitrate or a functional derivative thereof in an acidic medium such as for example hydrochloric acid in acetic acid, and preferably in the same reaction mixture, further reacting the thus obtained intermediate with a reagent of formula (VII) wherein L and E are as defined above, in the presence of a base such as, for example, sodium acetate.

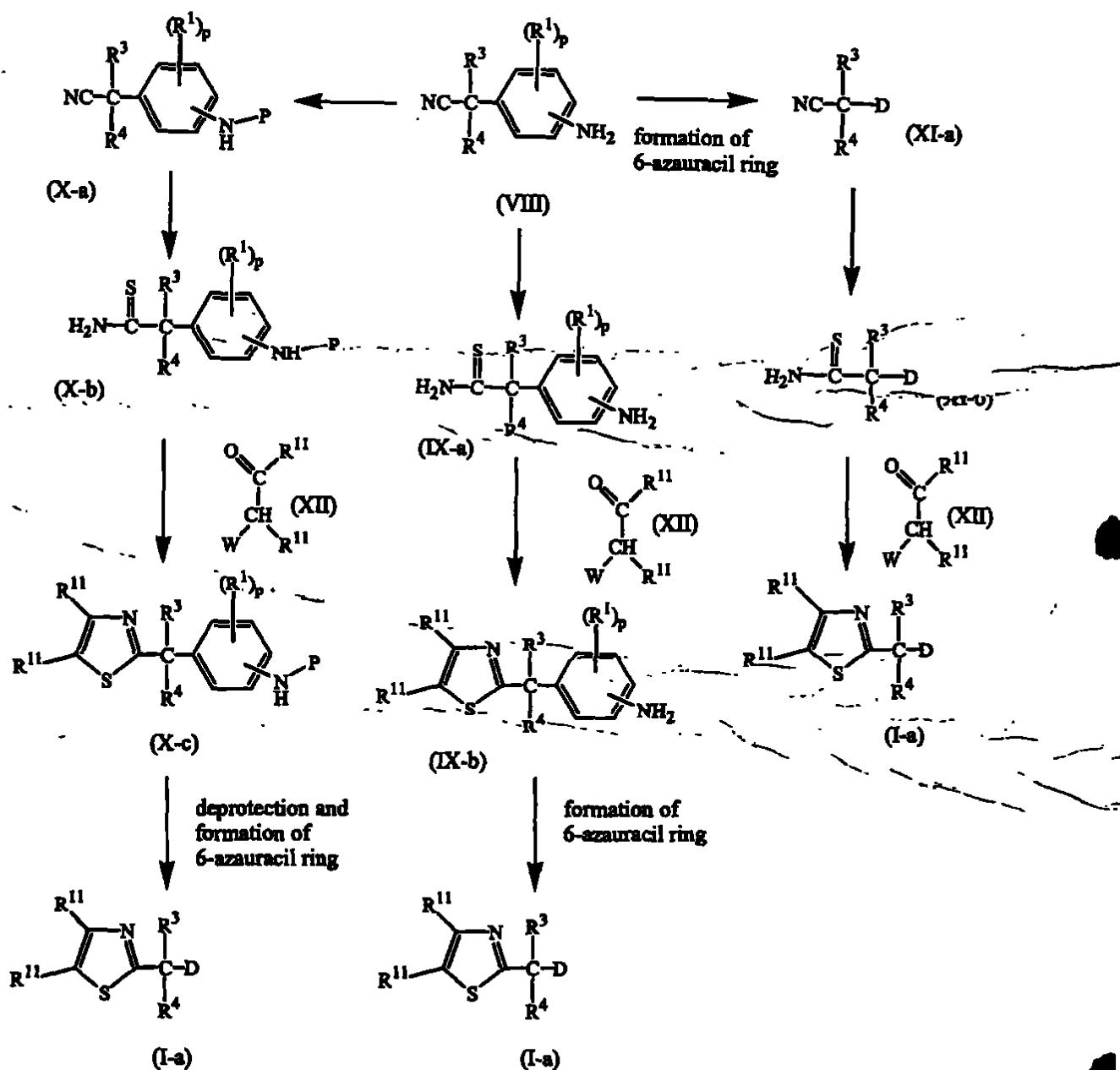


10 An interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R² is an optionally substituted 2-thiazolyl moiety, said compounds being represented by formula (I-a). The optionally substituted 2-thiazolyl moiety can be incorporated in the compounds of formula (I-a) at different stages of the preparation process.

15

For instance, scheme 1 above depicts three possible ways to prepare compounds of formula (I-a).

Scheme 1



A first pathway involves the reaction of the cyano moiety in an intermediate of formula (VIII) to the corresponding thioamide using H_2S gas in a suitable solvent such as, for example, pyridine and in the presence of a base such as, for example, triethylamine, thus obtaining an intermediate of formula (IX-a). This thioamide can then be cyclized with an intermediate of formula (XII) wherein W is a suitable leaving group such as, for example, a halogen, e.g. bromo, in a suitable solvent such as, for example, ethanol. The amino moiety in the resulting 2-thiazolyl derivative of formula (IX-b) can then be further reacted as described hereinabove to form a 6-azauracil ring, thus obtaining a compound of formula (I-a).

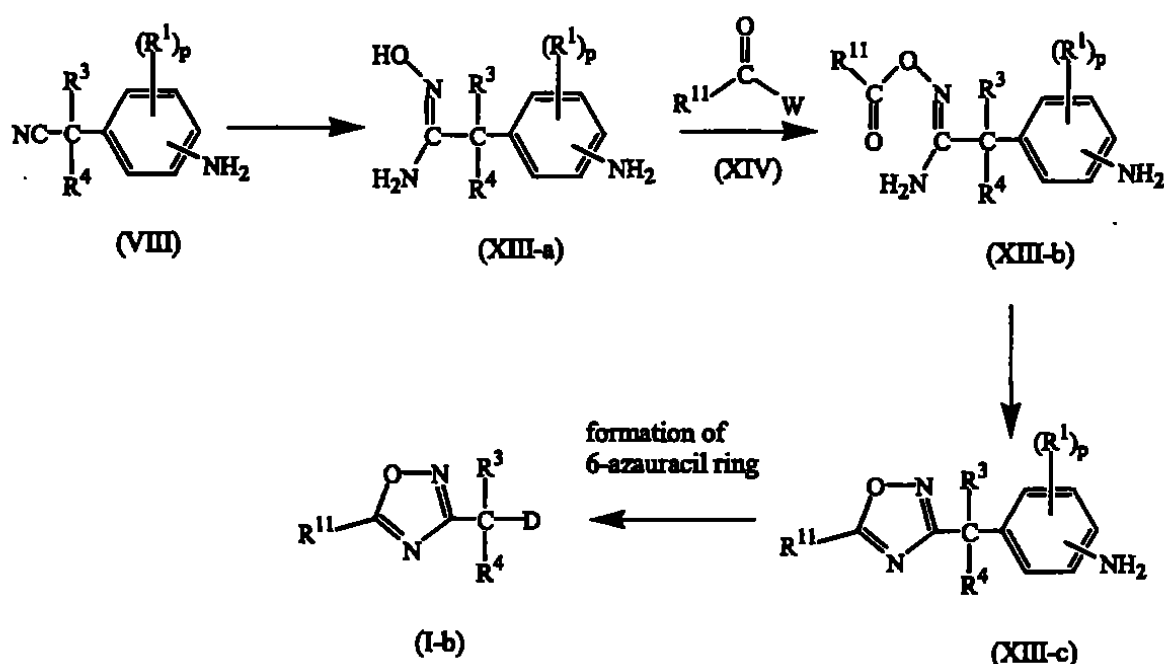
A second pathway to form compounds of formula (I-a) involves first the protecting of the amino moiety in an intermediate of formula (VIII) by introducing a suitable protective group P such as, for example, an alkylcarbonyl group, using art-known protection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (VII) can be reacted with the corresponding anhydride of formula alkyl-C(=O)-O-C(=O)-alkyl in an appropriate solvent such as, for example, toluene. The thus obtained intermediate of formula (X-a) can then be further reacted according to the first pathway described hereinabove. The final step, before formation of the 6-azauracil ring can be initiated after having deprotected the amino moiety using art-known deprotection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (X-c) may be deprotected by reacting them in a suitable solvent such as, for example, ethanol, in the presence of an acid such as, for example, hydrochloric acid.

A third pathway involves first the formation of the 6-azauracil ring as described hereinabove but starting from an intermediate of formula (VIII), and subsequently reacting the thus formed intermediate of formula (XI-a) with H₂S and further reacting the thioamide of formula (XI-b) with an intermediate of formula (XII) as described in the first pathway, to finally form a compound of formula (I-a).

Another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R² is an optionally substituted 1,2,4-oxadiazol-3-yl moiety, said compounds being represented by formula (I-b-1). The optionally substituted 1,2,4-oxadiazol-3-yl moiety can be incorporated at the same stages of the reaction procedure as depicted for the 2-thiazolyl derivatives in scheme 1.

For instance, analogous to one of the three pathways shown in scheme 1, compounds of formula (I-b-1) can be prepared by reacting an intermediate of formula (VIII) as depicted in scheme 2.

Scheme 2

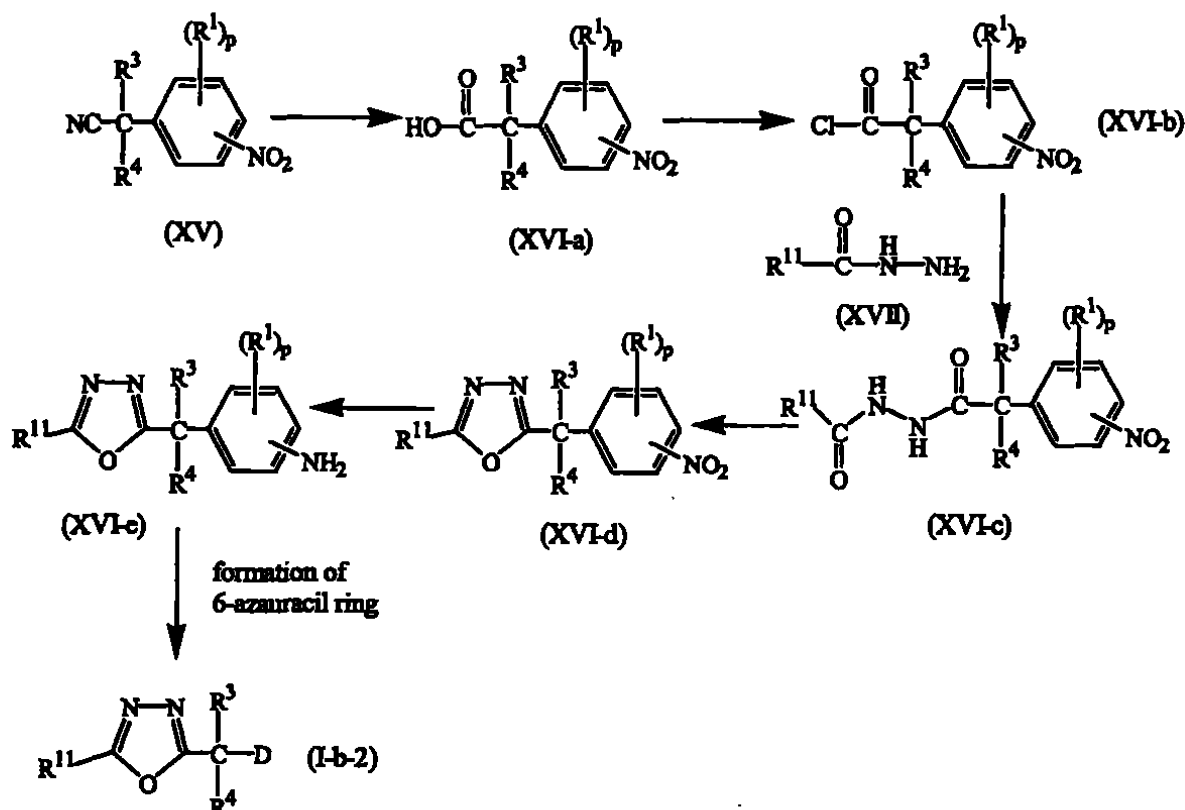


- In said scheme 2, the cyano group of an intermediate of formula (VIII) is reacted with hydroxylamine or a functional derivative thereof in a suitable solvent such as, for example, methanol, and in the presence of a base such as, for example sodium
- 5 methanolate. The thus formed intermediate of formula (XIII-a) is then reacted with an intermediate of formula (XIV) wherein W is a suitable leaving group such as, for example, a halogen, e.g. chloro, in an appropriate solvent such as, for example, dichloromethane, and in the presence of a base, such as, for example, *N,N*-(1-methyl-ethyl)ethaneamine. The resulting intermediate of formula (XIII-b) is then cyclized to a
- 10 3-oxadiazolyl derivative of formula (XIII-c). The amino moiety in the intermediates of formula (XIII-c) can then be transformed to the 6-azauracil ring as described above.

- Still another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R² is an optionally substituted 1,3,4-oxadiazol-2-yl moiety, said
- 15 compounds being represented by formula (I-b-2).

For instance, compounds of formula (I-b-2) can be prepared as depicted in scheme 3.

Scheme 3

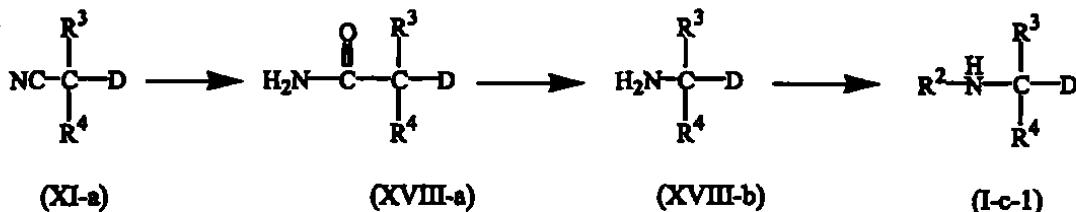


The nitrile moiety in an intermediate of formula (XV) is transformed into a carboxylic acid moiety using art-known techniques. For instance, the nitrile derivative may be refluxed in a mixture of sulfuric acid and acetic acid in water. The carboxylic acid

- 5 derivative of formula (XVI-a) may the further be reacted with a chlorinating agent such as, for example, thionyl chloride, to form an acylchloride derivative of formula (XVI-b). Subsequently, The acyl chloride may be reacted with a hydrazine derivative of formula (XVII) in a suitable solvent such as, for example, dichloromethane, and in the presence of a base such as, for example *N,N*-(1-methylethyl)ethaneamine. The thus formed
- 10 intermediate of formula (XVI-c) may be cyclized to a 1,2,4-oxadiazol-2-yl derivative of formula (XVI-d) in the presence of phosphoryl chloride. As a final step before the formation of the 6-azauracil ring as described above, the nitro group in the intermediates of formula (XVI-e) is reduced to an amino group using art-known reduction techniques such as, for instance, reducing the nitro group with hydrogen in methanol and in the
- 15 presence of a catalyst such as Raney Nickel.

Yet another interesting subgroup within the present invention are those compounds of formula (I) wherein $-X-R^2$ is $-NH-R^2$, said compounds being represented by formula (I-c-1). Scheme 4 depicts a suitable pathway to obtain compounds of formula (I-c-1).

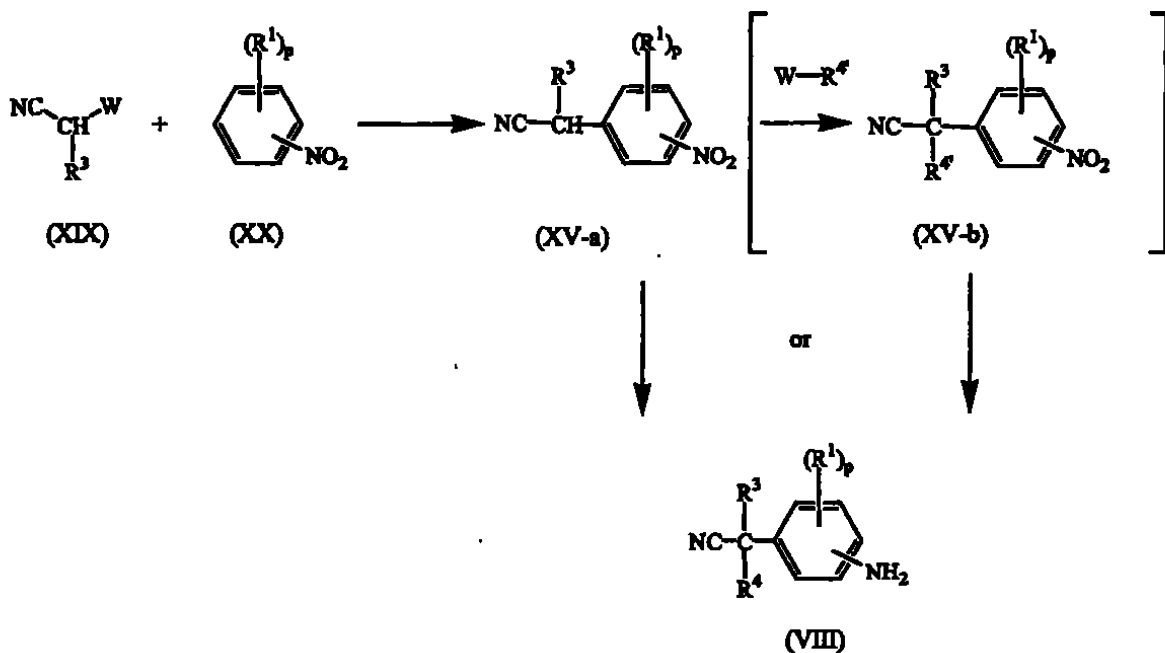
Scheme 4



- In said scheme 4, the cyano moiety of an intermediate of formula (XI-a) is hydrolyzed to the corresponding amide using art-known techniques such as, for instance, hydrolysis in the presence of acetic acid and sulfuric acid. The thus formed amide in the
- 5 intermediates of formula (XVIII-a) can be transformed in an amine using (diacetoxyiodo)benzene or a functional derivative thereof in a suitable solvent such as, for example a mixture of water and acetonitrile. The amine derivative of formula (XVIII-b) can then be reacted with benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate as described in Tetrahedron Letters No.14 (1975) p.
- 10 1219-1222 to obtain a compound, or with a functional derivative thereof such as, for instance, an isothiocyanate, in an appropriate solvent such as, for example, tetrahydrofuran.

- Intermediates of formula (VIII) can be prepared as depicted in scheme 5.
- 15

Scheme 5

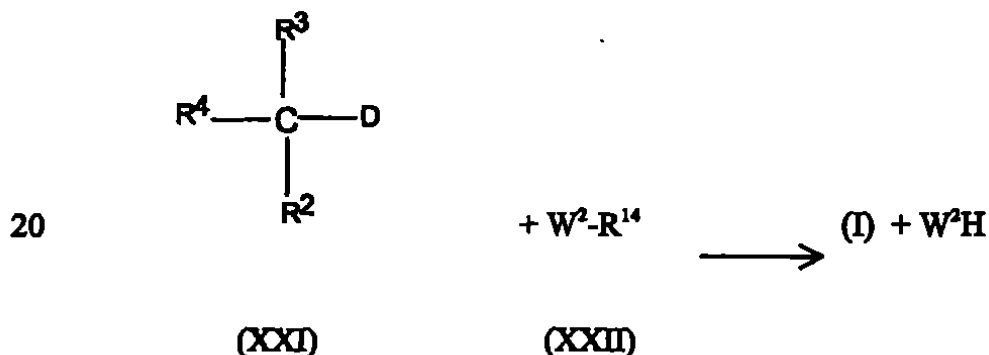


An intermediate of formula (XIX) and an intermediate of formula (XX) may be reacted

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in a suitable solvent such as, for example, dimethylsulfoxide, in the presence of a base such as, for example sodium hydroxide, to form an intermediate of formula (XV-a). The nitro moiety in the intermediates of formula (XV-a) may either be immediately reduced to an amino group using art-known reduction techniques such as, for example, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel, or may first be reacted with an intermediate of formula R^4-W wherein R^4 is the same as R^4 but other than hydrogen and W is a suitable leaving group such as, for example, a halogen, e.g. iodo, in a suitable solvent such as, for example, *N,N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, before reducing the nitro moiety.

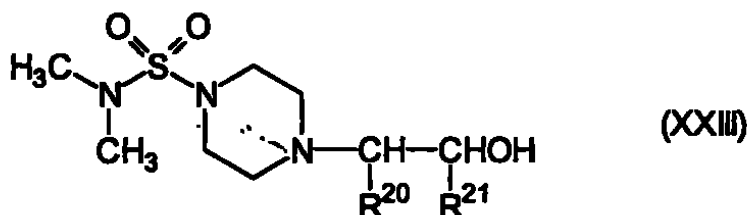
The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation such as, for example, those mentioned in WO99/02505 and the ones exemplified in the experimental part hereinafter. In particular, compounds of formula (I) containing at least one $-C(=O)-Z-R^{14}$ moiety born by R^2 , wherein Z is O or S and R^{14} is other than hydrogen, can suitably be prepared by reacting the compound of formula (XXI) containing the corresponding moiety $-C(=O)-Z-H$ with an appropriate reagent of formula (XXII) wherein W^2 is a suitable leaving group, as follows:



For instance a first process of such preparation involves reacting the compound of formula (XXI) containing the corresponding moiety $-C(=O)-Z-H$ with a halide, preferably a bromide having the formula $Br-R^{14}$, in a reaction-inert solvent such as defined above and in the presence of sodium hydrogenocarbonate. The said reaction is performed at a temperature below the boiling point of the solvent used and, for example, for a period of time between about 2 and 18 hours when dimethylformamide is used as the solvent. A second process of such preparation involves reacting the compound of

formula (XXI) containing the corresponding moiety – C(=O)-Z-H with an alcohol having the formula R¹⁴-OH, in a reaction-inert solvent such as defined above and in the presence of 1,1'-carbonylbis-1H-imidazole optionally admixed with 1,8-Diaza-7-bicyclo (5.4.0) undecene. When methylene chloride is used as the solvent, the reaction may be performed at room temperature for a period of time of several hours.

The present invention is also concerned with new compounds of formula :



- wherein R²⁰ and R²¹ are each independently selected from hydrogen or C₁₋₂₀ alkyl or R²⁰ and R²¹ taken together with the carbon atom to which they are attached form a cycloalkyl radical. These new compounds are useful for preparing a compound of formula (I) when Het⁵ represents a sulfonamido substituted piperazine. Such intermediate compounds of formula (XXIII) can be prepared by reacting N,N-dimethyl-1-piperazinesulfonamide with an alkylene oxide in a reaction-inert solvent such as methanol and/or methylene chloride. Suitable alkylene oxides for this purpose include for instance ethylene oxide, propylene oxide, 1-2 butylene oxide, cyclohexylene oxide and the like.
- The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *t*-butyl hydroperoxide. Suitable

solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

- 5 Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.
- 10 Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter
- 15 current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques,
- 20 e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

25

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

- 30 Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angiitis, eosinophilic fasciitis, eosinophilic pneumonia, PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.

The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergetically with eosinophils (Carr et al., 1994, Immunology, 91, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, Immunology Today, 15(3), 127-133).

The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, γ -interferon (IFN- γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

The selective chemokine inhibitory effect of the present compounds can be demonstrated by *in vitro* chemokine measurements in human blood. *In vivo* observations such as the inhibition of eosinophilia in mouse ear, the inhibition of blood eosinophilia in the *Ascaris* mouse model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA expression induced by anti-CD3 antibody in mice and the inhibition of allergen- or Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the usefulness of the present compounds in the treatment of eosinophil-dependent inflammatory diseases.

The present inhibitors of IL-5 production are particularly useful for administration via inhalation.

5 The intermediates of formula (XI-a) are interesting intermediates. Not only have they a particular usefulness as intermediates in the preparation of the compounds of formula (I), they also have valuable pharmacological activity.

10 In view of the above pharmacological properties, the compounds of formula (I) can be used as a medicine. In particular, the present compounds can be used in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned hereinabove, more in particular bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis.

15 In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from eosinophil-dependent inflammatory diseases, in particular bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to
20 warm-blooded animals, including humans.

The present invention also provides compositions for treating eosinophil-dependent inflammatory diseases comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

25

To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired
30 for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as parenteral administration; or topical administration such as via inhalation, a nose spray or the like. Application of said compositions may be by aerosol, e.g. with a propellant such as nitrogen, carbon

dioxide, a freon, or without a propellant such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

5

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

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In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6} alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β -CD; hydroxy C_{1-6} alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxy C_{1-6} alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6} alkylcarbonyl, particularly acetyl; C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or carboxy- C_{1-6} alkyloxy C_{1-6} alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6} alkylcarbonyloxy C_{1-6} alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, randomly methylated β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, 2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD

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(2-HP- β -CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl
5 and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the
10 M.S. ranges from 0.125 to 10.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges
15 from 0.125 to 3.

Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the compounds of the present invention need to be labelled, in particular by replacing,
20 partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having at least one ^{11}C -atom or tritium atom.

25 One particular group consists of those compounds of formula (I) wherein R^1 is a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g. ^{122}I , ^{123}I , ^{125}I , ^{131}I ; radioactive bromides, e.g. ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br , and radioactive
30 fluorides, e.g. ^{18}F . The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

Another interesting form of radiolabelling is by substituting a carbon atom by a ^{14}C -atom or the substitution of a hydrogen atom by a tritium atom.

Hence, said radiolabelled compounds of formula (I) can be used in a process of specifically marking receptor sites in biological material. Said process comprises the steps of (a) radiolabelling a compound of formula (I), (b) administering this radiolabelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound. The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.

The radiolabelled compounds of formula (I) are also useful as agents for screening whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.

When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

In general, it is contemplated that a therapeutically effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

Experimental part

In the examples hereinafter, "DMSO" stands for dimethylsulfoxide, "RT" stands for room temperature, "DMF" stand for *N,N*-dimethylformamide, "EtOAc" stands for ethylacetate, "DIPE" stands for diisopropylether and "THF" stands for tetrahydrofuran.

A. Preparation of the intermediate compounds

Example A1

a) A mixture of 2-chloropropionitrile (0.2 mol) and 1,3-dichloro-5-nitrobenzene (0.2 mol) in DMSO (50ml) was added dropwise at RT to a solution of NaOH (1 mol) in DMSO (150ml) while the temperature was kept below 30°C. The mixture was stirred at RT for 1 hour, then poured out on ice and acidified with HCl. The precipitate was filtered off, washed with H₂O and taken up in CH₂Cl₂. The organic solution was washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 70/30). The pure fractions were collected and the solvent was evaporated, yielding 19.5 g (40%) of (±)-2,6-dichloro-α-methyl-4-nitrobenzeneacetonitrile (interm. 1).

b) NaH 80% (0.0918 mol) was added portionwise at 0°C under N₂ flow to a solution of intermediate (1) (0.0612 mol) in DMF (100ml). The mixture was stirred at 0°C under N₂ flow for 1 hour. CH₃I (0.0918 mol) was added dropwise at 0°C. The mixture was stirred at 50°C for 12 hours, then poured out on ice and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated, yielding 17.1g of 2,6-dichloro-α,α-dimethyl-4-nitrobenzeneacetonitrile (interm. 2).

c) A mixture of intermediate (2) (0.066 mol) in CH₃OH (200ml) was hydrogenated at RT under a 3 bar pressure for 1 hour with Raney Nickel (15g) as a catalyst. After uptake of H₂, the catalyst was filtered through celite, washed with CH₃OH and the filtrate was evaporated, yielding 17.1g of 4-amino-2,6-dichloro-α,α-dimethylbenzeneacetonitrile (interm. 3).

Example A2

- 5 a) A solution of NaNO_2 (0.36 mol) in H_2O (50 ml) was added to a solution of intermediate (3) (0.34 mol) in acetic acid (700 ml) and HCl (102 ml), stirred at 10°C . The reaction mixture was stirred for 80 minutes at 10°C . A powdered mixture of sodium acetate (1.02 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.374 mol) was added and the reaction mixture was stirred for 40 minutes. The reaction mixture was poured out onto crushed ice. The precipitate was filtered off, washed with
- 10 water, taken up into CH_2Cl_2 , and the layers were separated. The organic layer was dried, filtered and the solvent evaporated, yielding 138.5 g (84%) of diethyl *N,N'*-[2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]dicarbamate (interm. 4).
- 15 b) A solution of intermediate (4) (0.28 mol) and potassium acetate (0.28 mol) in acetic acid (1000 ml) was stirred and refluxed for 3 hours. The reaction mixture containing ethyl [[2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 5) was used as such in the next step.
- 20 c) Intermediate (5) (crude reaction mixture) was treated with HCl 36% (0.84 mol). The reaction mixture was stirred and refluxed for 4 hours, then stirred at RT over the weekend. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated, yielding 111.6 g of 2-[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-
- 25 2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 6).
- d) A suspension of intermediate (6) (0.28 mol) in mercaptoacetic acid (250.0 ml) was stirred for 4 hours at 100°C , then allowed to cool to RT and stirred overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with
- 30 CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue was purified by short column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2). The pure fractions were collected and the solvent was evaporated. The residue was stirred in

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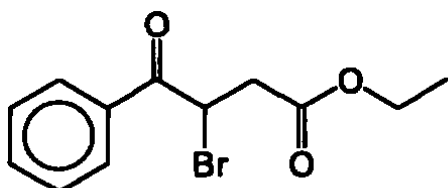
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DIPE, filtered off, washed with DIPE, then dried, yielding 36.8 g (41%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α,α -dimethylbenzeneacetonitrile. The filtrate was stirred in DIPE and the resulting precipitate was filtered off, washed with DIPE, and dried, yielding 2.5 g (3%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α,α -dimethylbenzeneacetonitrile (interm. 7).

e) A solution of intermediate (7) (0.107 mol) and *N,N*-bis(1-methylethyl)ethanamine (0.315 mol) in pyridine (500 ml) was stirred and heated to 80°C. H_2S was allowed to bubble through this solution for 24 hours at 80°C. H_2S gas inlet was stopped and the reaction mixture was stirred over the weekend at RT. The solvent was evaporated. CH_2Cl_2/CH_3OH (500 ml; 9:1) was added, and this mixture was poured out into 2 N HCl (1000 ml) at 0°C. The mixture was stirred for 10 minutes. The precipitate was filtered off and dried, yielding 23.2 g (64%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4)- α,α -dimethylbenzeneethanethioamide (interm. 8).

Example A3

Reaction under N_2 atmosphere. A solution of intermediate (8) (0.0125 mol) and



(0.0157 mol) in ethanol (60 ml) and DMF (30 ml;

dried over molecular sieves) was stirred for 6.5 hours at 60 °C, then overnight at RT. The solvent was evaporated. The residue was taken up into water (100 ml) and this mixture was extracted with CH_2Cl_2 (100 ml). The separated organic layer was dried ($MgSO_4$), filtered and the solvent evaporated, then co-evaporated with toluene. The residue (13 g) was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0, then 99/1, ending with 98/2). The desired fractions were collected and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue (6.5 g) was crystallized from CH_3CN . The precipitate was filtered off, washed with CH_3CN and DIPE, then dried (vacuum, 50 °C), yielding 3.17 g (46.5 %) of ethyl-2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl]phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetate (intermediate 9) having a

melting point of 148°C.

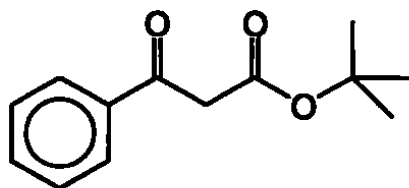
Example A4

- 5 A mixture of intermediate (9) (0.00183 mol) and NaOH 1N (0.0055 mol) in CH₃OH (25 ml) and THF (25 ml) was stirred overnight at RT. The reaction mixture was acidified with 1N HCl (8 ml), and the product was taken up into EtOAc. The organic layer was washed with brine, dried, filtered and the solvent was evaporated. The residue was crystallized from CH₃CN. The precipitate was filtered off, washed with
- 10 DIPE, and dried, yielding 0.8 g (79%) of 2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetic acid (intermediate (10)).

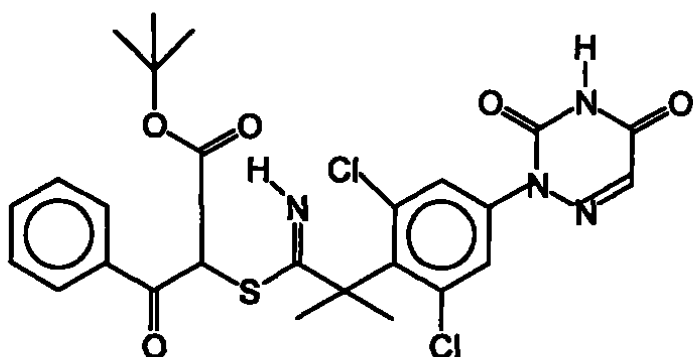
Example A5

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First a solution of bromine (0.02 mol) in CH₂Cl₂ (20 ml) was added dropwise at 10°C under N₂ flow to a mixture of a compound of formula

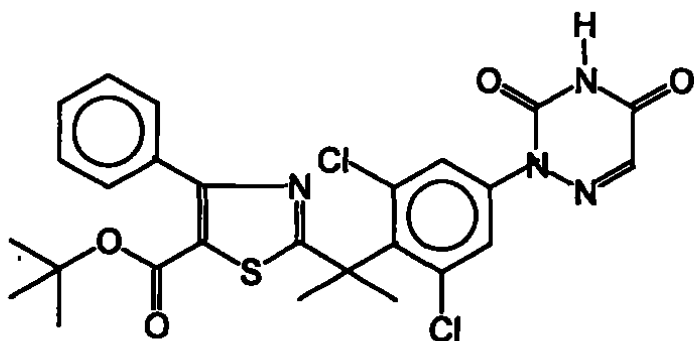


- (0.0227 mol) in CH₂Cl₂ (50ml). The mixture was stirred at 10°C for 1 hour. H₂O and
- 20 solid K₂CO₃ were added. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The reaction was carried out 4 times, using the same quantities and combining the residues yielding 14 g (51%) of 1,1-dimethylethyl α-bromo-β-oxo-benzenepropanoate. A mixture of intermediate (8) (0.0119 mol), 1,1-dimethylethyl α-bromo-β-oxo-benzenepropanoate (0.0137 mol) and K₂CO₃ (0.0357
- 25 mol) in CH₃CN (55ml) was stirred at room temperature for 3.5 hours. Ice and EtOAc were added. The mixture was acidified with HCl 3N. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The product was used without further purification. Yielding: 8g of intermediate 11 having the formula



Example A6

- 5 Intermediate (11) (0.0119 mol) and tert.-butanol (24g) were stirred and refluxed for 2 hours. The mixture was brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . The organic solution was washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (7.8g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1; 15-40 μm). Two
- 10 fractions were collected and their solvents were evaporated. Yielding: 2.66g (fraction 1) and 0.7g fraction 2 (50%). Fraction 2 was purified by column chromatography over C 18 (eluent: $\text{CH}_3\text{OH}/\text{NH}_4\text{OAc}$ 0.5% 80/20; column: HYPERSIL C 18 3 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.45g of intermediate
- 12 having a melting point of 130°C and represented by the formula

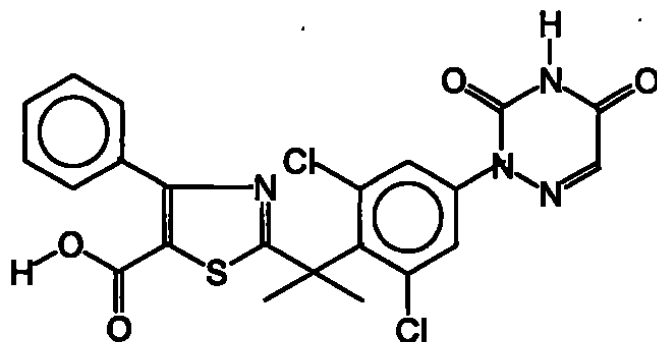


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Example A7

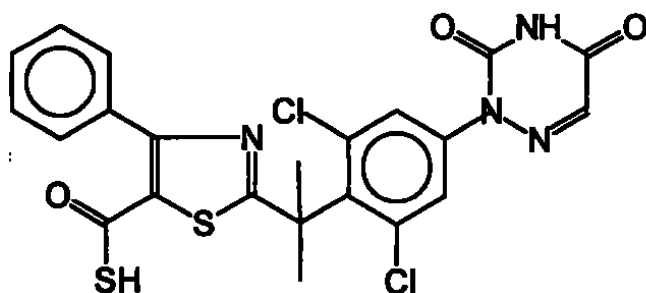
- Intermediate 12 (0.00465 mol) was added portionwise at 0°C - 10°C to trifluoroacetic acid (35ml). The mixture was stirred at room temperature for 3 hours and poured out
- 20 into H_2O . The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2 .

The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.4g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 97/3/0.2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN . The precipitate was filtered off and dried. Yielding: 1.16g of intermediate 13 having a melting point of 232°C and represented by the formula



10 Example A8

1,1'-carbonylbis-1H-imidazole (0.0159 mol) was added portionwise at RT under N_2 flow to a solution of intermediate (13) (0.00795 mol) in DMF (60 ml). The mixture was stirred at RT overnight. H_2S was bubbled through the mixture for 1 hour. The mixture was stirred at RT for 1 hour, poured out into a saturated NaCl solution and extracted twice with CH_2Cl_2 . The combined organic layer was dried (MgSO_4), filtered and the solvent was evaporated. The product, intern.14 represented by the formula

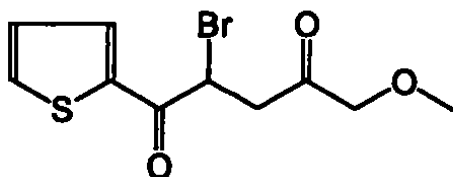


was used without further purification.

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Example A9

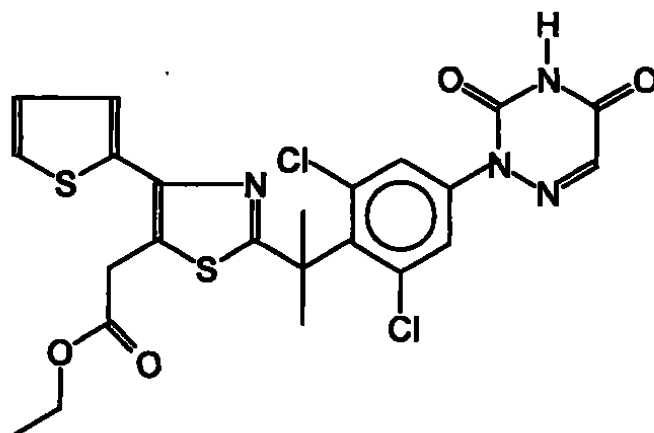
A mixture of intermediate (8) (0.0158 mol) and



(0.0237 mol) in ethanol (60ml) and DMF (40ml)

- 5 was stirred at 60°C for 4 hours. The solvent was evaporated. EtOAc was added. The organic solution was washed 3 times with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. The residue (11.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. Yielding: 4.2g (47%). Part of this fraction (1.5g) was
- 10 crystallized from petroleum ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.15g of intermediate 15 having a melting point of 126°C and represented by the formula

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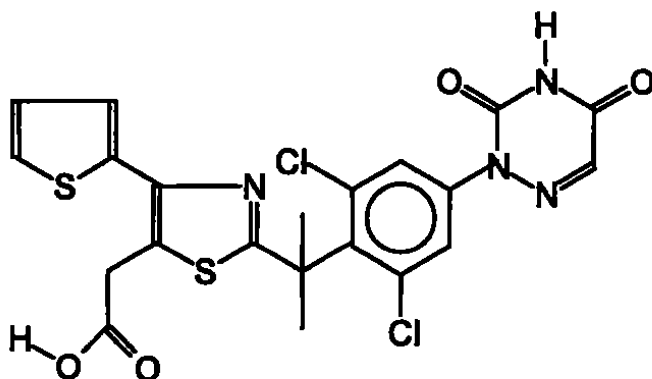
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Example A10

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- A mixture of intermediate (15) (0.0045 mol) and NaOH (0.0135 mol) in methanol (30ml) and THF (30ml) was stirred at room temperature for 12 hours, poured out on ice, acidified with HCl and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.2g) was purified by
- 30 column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.1; 15-40

μm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.5g (64%). Part of this fraction (1g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.5g of intermediate 16 having a melting point of 192°C and represented by the formula



Example A11

a) NaOCH₃, 30% (0.592 mol) was added to a solution of hydroxylamine hydrochloride (0.1085 mol) in CH₃OH (200 ml), stirred at RT. The mixture was stirred for 10 minutes. Intermediate (3) (0.0542 mol) was added portionwise and the resulting reaction mixture was stirred and refluxed overnight. The solvent was evaporated. The residue was partitioned between CH₂Cl₂ and water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, and dried, yielding 3.7 g of (26%) 4-amino-2,6-dichloro-N'-hydroxy- α,α -dimethylbenzeneethanimidamide (interm. 17).

b) A solution of intermediate (17) (0.0323 mol) and *N,N*-bis(methylethyl)ethanamine (0.0339 mol) in CH₂Cl₂ (190 ml) was stirred at 15°C. A solution of 2-methylbenzoyl chloride (0.0323 mol) in CH₂Cl₂ (10 ml) was added dropwise and the resulting reaction mixture was stirred for one hour. Water was added. The organic layer was separated, dried, filtered and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 13.0 g of [1-amino-2-(4-amino-2,6-dichlorophenyl)-2-methylpropylidenyl]amino 2-methylbenzoate (interm. 18).

c) A solution of intermediate (18) (0.0323 mol) and *p*-toluenesulfonic acid (0.0323 mol) in DMSO (100 ml) was stirred for 30 minutes at 150°C. The reaction

mixture was cooled. Water was added and this mixture was extracted with toluene. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2). The desired fractions were collected and the solvent was evaporated. The concentrate was co-
5 evaporated with EtOAc, yielding 11.7 g of 3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]benzenamine (interm. 19).

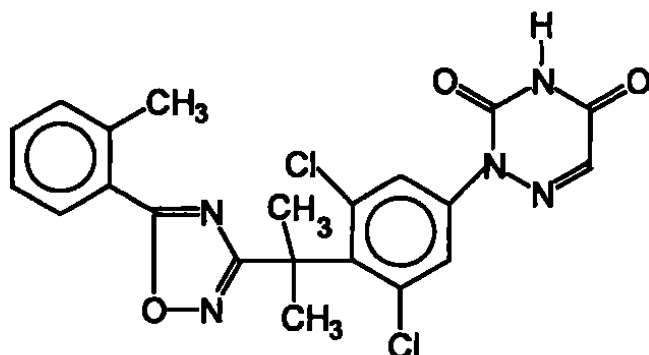
d) A solution of intermediate (19) (0.0302 mol) and HCl conc. (0.0906 mol) in acetic acid (100 ml) was stirred at 0°C . A solution of NaNO_2 (0.032 mol) in water (10 ml)
10 was added dropwise at 0°C . The reaction mixture was stirred for 1 hour at 0°C . A powdered mixture of sodium acetate (0.0906 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.0332 mol) was added portionwise. The mixture was allowed to warm to RT and stirred for 1 hour. Water was added and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent
15 evaporated, yielding diethyl *N,N*-[2-[[3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]-dicarbamate (interm. 20).

e) A solution of intermediate (20) (0.0302 mol) and sodium acetate (0.0302 mol) in
20 acetic acid (200 ml) was stirred and refluxed for 3 hours. The reaction mixture was poured out into water and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding ethyl [[2-[3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-
25 1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 21).

f) A mixture of intermediate (21) (0.0302 mol) in HCl 36% (10 ml) and acetic acid (200 ml) was stirred and refluxed overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH_2Cl_2 . The separated organic layer
30 was dried, filtered and the solvent evaporated, yielding 16.3 g of 2-[3,5-dichloro-4-[1-[5-[2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 22).

Example A12

A mixture of intermediate (22) (0.0133 mol) in mercaptoacetic acid (7ml) was stirred at 175°C for 2 hours. The mixture was cooled, poured out into ice water, basified with K₂CO₃ and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and the solvent was evaporated, yielding 2.2g (36%) of intermediate 23 represented by the formula



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Example A13

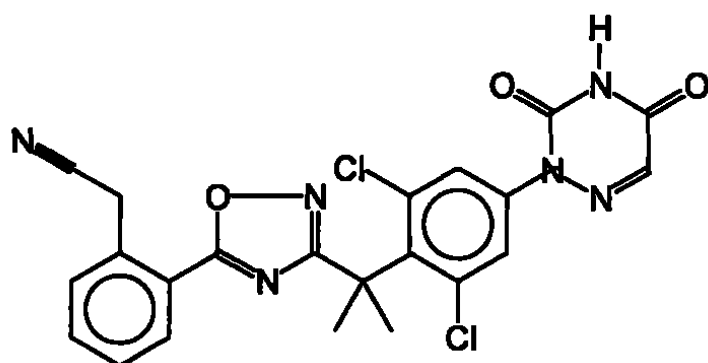
A mixture of intermediate (23) (0.0011 mol), 1-bromo-2,5-pyrrolinedione (0.0011 mol) and dibenzoyl peroxide (catalytic quantity) in CCl₄ (30 ml) was stirred and refluxed for 3 hours. The mixture was allowed to cool to RT. The mixture was filtered over dicalite and the filtrate contained 2-[4-[1-[5-[2-(bromomethyl)phenyl]-1,2,4-oxadiazol-3-yl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione (intermediate 24).

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Example A14

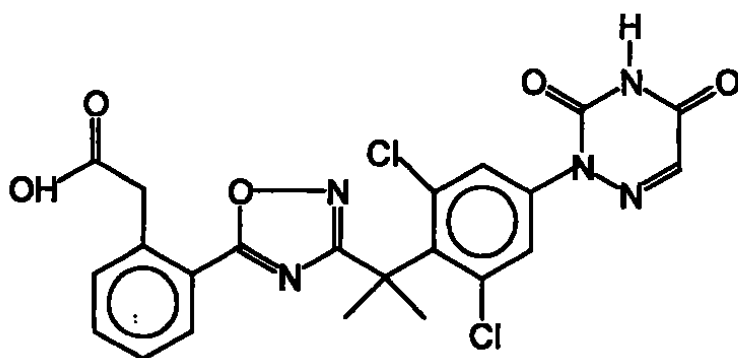
A solution of intermediate (24) (0.017 mol) and KCN (0.034 mol) in ethanol (100 ml) and H₂O (30 ml) was stirred for 8 hours at 60°C. The solvent was evaporated under reduced pressure. The residue was taken up into CH₂Cl₂, then washed with water, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 8.2 g of interm.25 represented by the formula

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Example A15

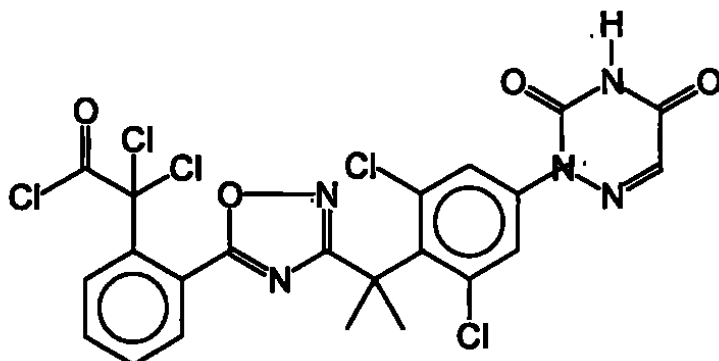
- 5 A solution of intermediate (25) (0.017 mol) in HOAc (50 ml), H₂SO₄ (50 ml) and H₂O (50 ml) was stirred and refluxed for 2 hours. The reaction mixture was poured out into ice-water and the resulting precipitate was filtered off, washed, then dissolved in CH₂Cl₂. The organic solution was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 95/5). The
- 10 desired fractions were collected and the solvent was evaporated. The residue was purified by high performance liquid chromatography over RP BDS Hyperprep C18 (100 Å, 8 µm; gradient elution with (0.5% NH₄OAc in water/CH₃CN 90/10)/CH₃OH/CH₃CN). The pure fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off and dried (vacuum, 60 °C).
- 15 Yield: 0.084 g of intermediate 26 represented by the formula



Example A16

- A solution of intermediate (26) (0.0014 mol) in SOCl₂ (15 ml) was stirred and refluxed
- 20 for 1 hour. SOCl₂ was evaporated under reduced pressure. Toluene was added and azeotroped on the rotary evaporator, yielding 100% of intermediate 27 represented by

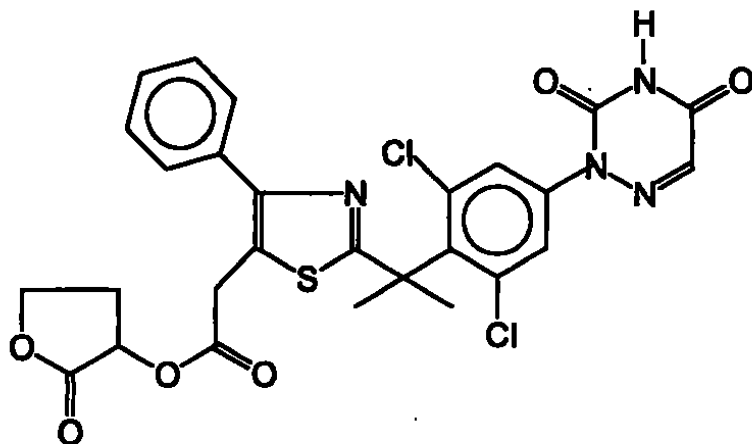
the formula



B. Preparation of the final compounds

5 Example B1

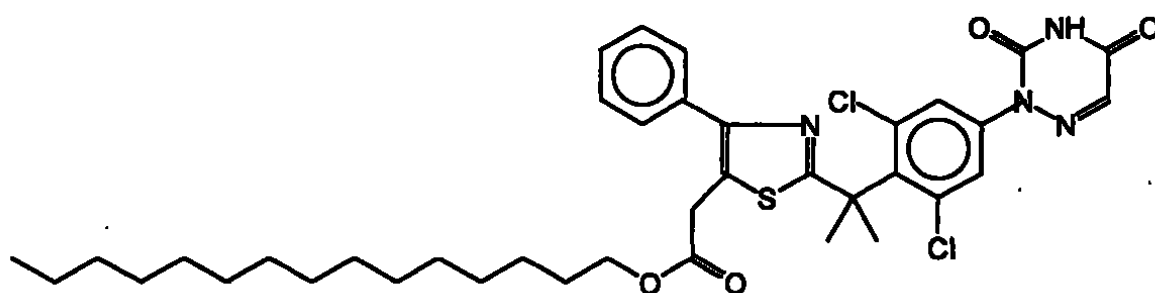
A mixture of 3-bromodihydro-2(3H)-furanone (0.0081 mol) in DMF (16ml) was added dropwise at room temperature to a mixture of intermediate (10) (0.00773 mol) and NaHCO_3 (0.0081 mol) in DMF (30ml). The mixture was stirred at 70°C for 5 hours and brought to room temperature. H_2O and a saturated NaCl solution were added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried. Yielding: 1.24g compound 1 having a melting point of 72°C and represented by the formula



Example B2

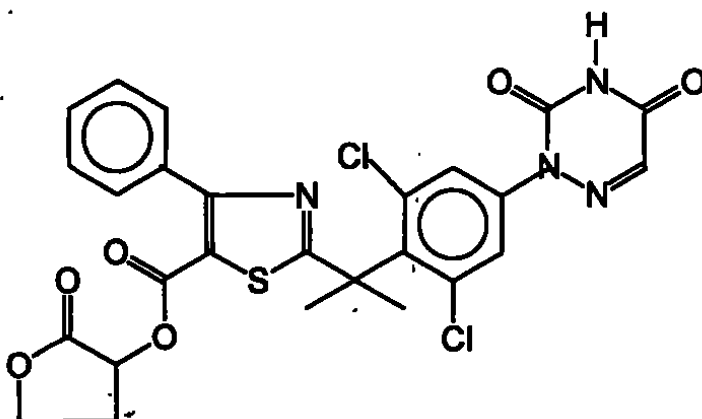
20 A solution of 1-bromopentadecane (0.0051 mol) in DMF (18ml) was added dropwise at

room temperature to a mixture of intermediate (10) (0.00483 mol) and NaHCO_3 (0.0051 mol) in DMF (10ml). The mixture was stirred at 70°C for 5 hours and at 45°C overnight, then brought to room temperature. H_2O and NaCl was added. The mixture was extracted with EtOAc. The organic layer was separated, washed with a saturated NaCl solution, dried (MgSO_4), filtered and the solvent was evaporated. The residue (3.8g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.49g compound 2 having a melting point of 80°C and represented by the formula



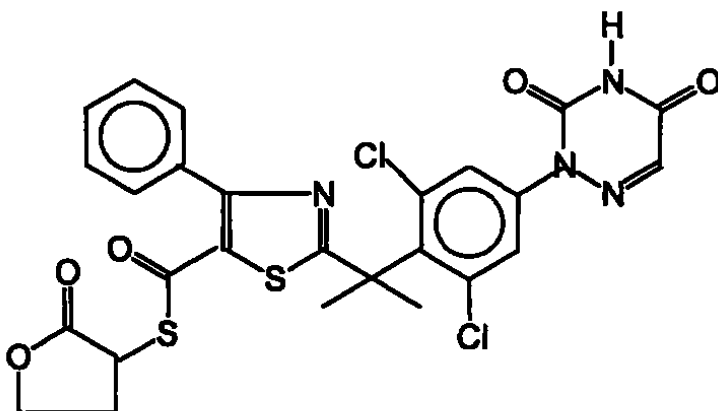
Example B3

A solution of 3-bromodihydro-2(3H)-furanone (0.0073 mol) in DMF (12ml) was added dropwise at RT to a mixture of intermediate (13) (0.00695 mol) and NaHCO_3 (0.0073 mol) in DMF (22ml). The mixture was stirred at 70°C for 2.5 hours, brought to RT and poured out into H_2O . The precipitate was filtered off and taken up in CH_2Cl_2 . The organic layer was separated, washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (5.4g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN , diethyl ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.3g. This fraction was recrystallized from CH_3CN , 2-propanone and diethyl ether. The precipitate was filtered off and dried. Yielding: 0.89g compound 3 having a melting point of 208°C and represented by the formula



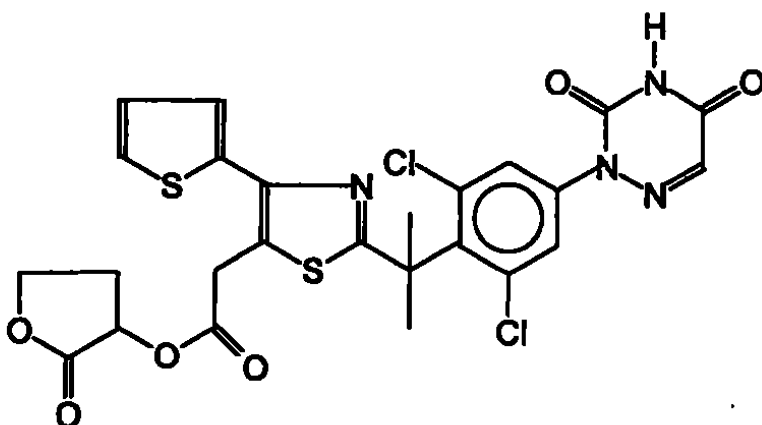
Example B4

- 5 NaHCO_3 (0.00835 mol) was added dropwise at 5°C under N_2 flow to a mixture of intermediate (14) (0.00795 mol) in DMF (22ml). Then a solution of 3-bromodihydro-2(3H)-furanone (0.00835 mol) in DMF (12ml) was added dropwise. The mixture was brought to RT and stirred at RT for 30 min and then poured out into H_2O and a saturated NaCl solution. A small amount of HCl 3N was added. The precipitate was filtered off
- 10 and taken up in CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (5.1g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98.5/1.5; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN , diethyl ether and DIPE. The precipitate was filtered off and dried. The residue was
- 15 recrystallized from CH_3CN , diethyl ether and DIPE. The precipitate was filtered off and dried. Yielding: 0.85g compound 4 having a melting point of 212°C and represented by the formula



Example B5

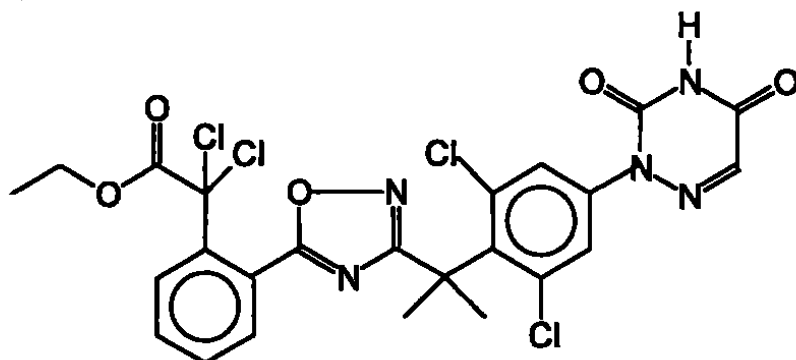
A mixture of 3-bromodihydro-2(3H)-furanone (0.00172 mol) in DMF (5ml) was added dropwise at RT to a mixture of intermediate (16) (0.00172 mol) and NaHCO₃ (0.00172 mol) in DMF (5ml). The mixture was stirred at 70°C for 5 hours, poured out into H₂O and a saturated NaCl solution and extracted with EtOAc. The organic layer was separated, washed several times with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. The residue was purified again by column chromatography over silica gel (eluent: CH₂Cl₂/2-propanol 97/3; 15-40 μm). The desired fractions were collected and the solvent was evaporated. Yielding: 0.13g compound 5 having a melting point of 110°C and represented by the formula



Example B6

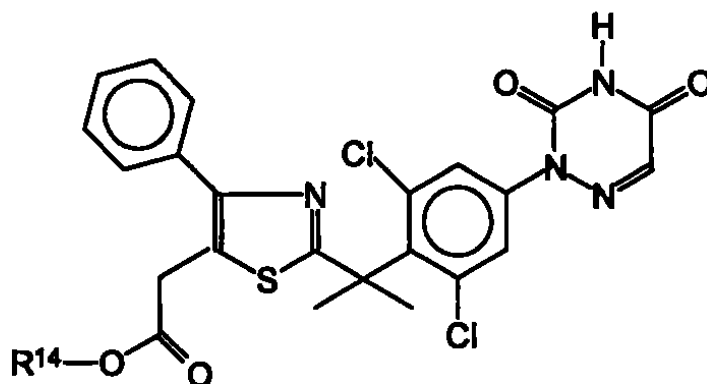
A solution of intermediate (27) (0.001 mol) in ethanol (15 ml) and dichloromethane (15 ml) was stirred and refluxed for one hour. The solvent was evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by HPLC over Hyperprep C18 (eluent: ((0.5% NH₄OAc in H₂O)/CH₃CN 90/10)/CH₃CN (0 min) 80/20, (44 min) 20/80, (57-61 min) 0/100). The desired fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off, washed and dried (vacuum, 60 °C). Yield: 0.059 g compound 6 having a melting point of 157°C and

represented by the formula



Example B7

- 5 A mixture of intermediate (10) (0.00387 mol) and 1,1'-carbonylbis-1H-imidazole (0.0058 mol) in dichloromethane (40ml) was stirred at RT for 90 minutes, then cyclohexylmethanol (0.0058 mol) was added. The mixture was stirred at RT overnight, diluted with CH_2Cl_2 and washed twice with an aqueous solution of NaCl. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The
- 10 residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50/50). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate was filtered off, washed with DIPE and dried at 50°C overnight. Yielding: 1.43g compound 7 with a molecular weight of 613.5, a melting point of 180°C and represented by the formula



IA

15

wherein R^{14} is cyclohexylmethyl.

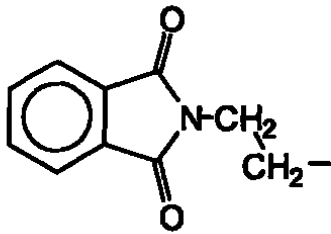
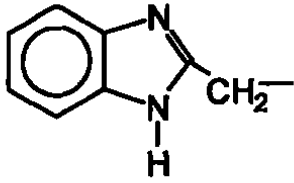
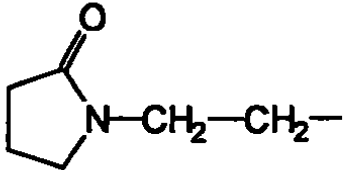
Examples B8 to B53

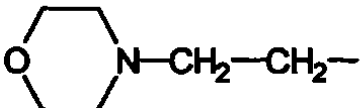
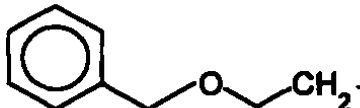
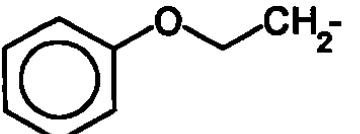
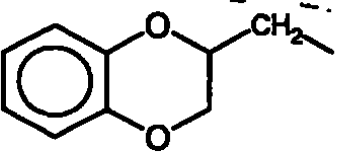
- 20 The following table 1 lists compounds of formula (IA) which were prepared according to the procedure of example B7, while replacing cyclohexylmethanol by the relevant

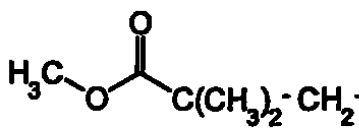
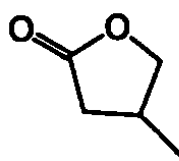
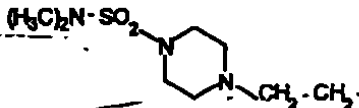
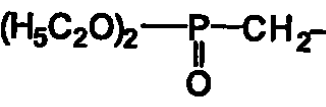
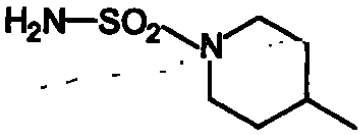
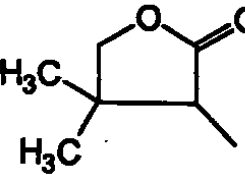
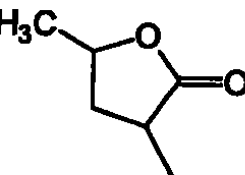
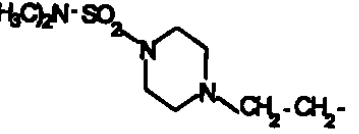
alcohol having the formula $R^{14}OH$. For the synthesis of compounds 8, 15-18, 21-23, 27, 32-34, 40-42 and 44, the amount of dichloromethane was increased up to 50 ml, and for compound 53 up to 60 ml. For the synthesis of compound 51, dichloromethane was replaced by 45 ml DMF. This table also indicates the melting point (when available)

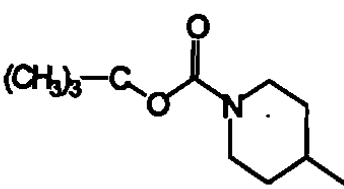
5 M.P.(expressed in °C) and the yield Y of obtention (expressed as a percentage) of the said compounds.

TABLE 1

<u>COMPOUND NO.</u>	<u>R¹⁴</u>	<u>M.P. (°C)</u>	<u>Y (%)</u>
8			
9	Isopentyl	148	
10	2-phenyl-ethyl	130	38
11	3-phenyl-n-propyl	114	41
12	2-(N,N'-diisopropylamino)-ethyl	136	
13	2-cyano-ethyl	179	62
14			75
15	3-cyclohexyl-n-propyl	130	
16	4-phenyl-n-butyl	128	
17	Cyclopentylmethyl		
18	3-cyclopropyl-n-propyl		
19			50

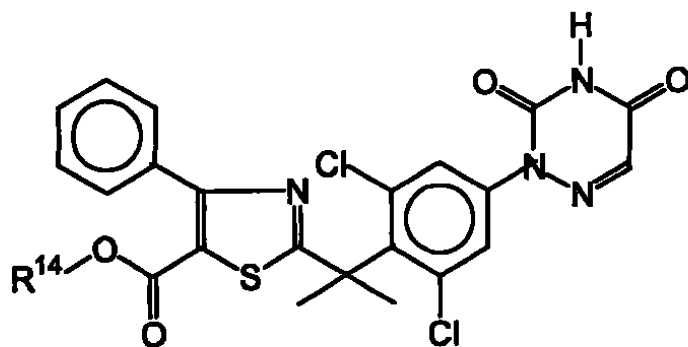
COMPOUND NUMBER	R ¹⁴	M.P. °C	Y(%)
20			
21	5-phenyl-n-pentyl	155	
22	Cyclobutylmethyl	150	
23	2-cyclohexylethyl	150	
24			56
25	Cyclopentylmethyl	160	
26	2-isopentenyl	175	
27	1-Cyanoethyl		
28			
29	4-Cyclohexyl-n-butyl		
30			33
31	2,2,2-trifluoroethyl		67
32	Phenylmethyl		
33	Phenyl		
34	2-methoxyethyl		
35	3-ol-n-propyl		
36	Acetamido	246	29
37	N,N'-diethylacetamido	162	60
38	Dimethylaminoethyl		
39	Styrylmethyl		
40	Cyclohexyl	183	17

COMPOUND NUMBER	R ¹⁴	M.P.°C	Y(%)
41	Toluylacetyloxy	151	71
42		140	37
43	N-methylpiperidinyI		28
44		160	
45			22
46		156	49
47		191	37
48	2,2-diethoxyethyl	156	
49			19
50	Benzylaminoethyl		
51			40
52			22

COMPOUND NUMBER	R ¹⁴	M.P.°C	Y(%)
53			43

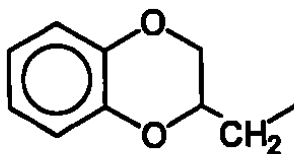
Example B 54

- 5 A mixture of 2-bromomethyl-1,4-benzodioxan (0.0044 mol) in DMF (2 ml) was added to a mixture of intermediate (13) (0.0044 mol) and NaHCO₃ (0.0044 mol) in DMF (8 ml). The mixture was stirred at 70°C for 6 hours, then 0.0022 mol of intermediate (13) was added. The mixture was stirred again at 70°C overnight, then poured out into H₂O, acidified with HCl (3N), extracted with EtOAc and washed with H₂O. The organic layer
- 10 was separated, dried, filtered and the solvent was evaporated. The residue (3.9 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from CH₃CN/DIPE. The precipitate was filtered off and dried, yielding 0.57 g compound 54 having a molecular weight of 651.5, identified in table 2
- 15 below and represented by the formula



IB

wherein R¹⁴ is



Example B 55

A mixture of bromo-1 phenyl -2 ethane (0.0065 mol), intermediate (13)(0.0050 mol) and NaHCO_3 (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then poured out on ice, acidified with HCl (3N) until pH 5, extracted with EtOAc and washed with H_2O several times. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (3.2 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1; 70-200 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.6 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.42 g compound 55 of formula (IB), having a molecular weight of 607.5 and identified in table 2 below.

Example B 56

A mixture of phenylbromomethane (0.0065 mol), intermediate (13) (0.0050 mol) and NaHCO_3 (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then cooled and poured out on ice. The precipitate was filtered, washed with H_2O and the solvent evaporated. The residue was taken up in HCl (diluted) then H_2O . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (3.0 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99.5/0.5; 70-200 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.9 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.51 g compound 56 of formula (IB), having a molecular weight of 593.5 and identified in table 2 below.

Example B 57

A mixture of tert-butyl bromoacetate (0.0060 mol), intermediate (13)(0.0050 mol) and NaHCO_3 (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then cooled and poured out into ice water. The precipitate was filtered, washed with H_2O , centrifugated off and taken up in EtOAc. The organic layer was separated, washed with water, dried (MgSO_4), filtered and the solvent was evaporated. The residue (3.0 g) was

93
purified by column chromatography over silica gel (eluent: CH_2Cl_2 ; 70-200 μm). Two fractions were collected and their solvents were evaporated. The first fraction (0.9 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.53 g compound 57 of formula (IB), having a molecular weight of 617.5 and identified in table 2 below.

Example B 58

10 A mixture of cyclopropyl bromomethane (0.0040 mol) in DMF (10 ml) was added dropwise at RT to a mixture of intermediate (13) (0.0040 mol) and NaHCO_3 (0.0040 mol) in DMF (10 ml). The mixture was stirred at 70°C for 5 hours, poured out on ice, neutralized slowly with HCl (3N) and extracted with EtOAc. The organic layer was separated, washed several times, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.8 g) was purified by column chromatography over silica gel
15 (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 92/8; 15-40 μm ; $\text{CH}_3\text{CN}/\text{NH}_4\text{Ac}$ 1% 60/40 10 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.34 g compound 58 of formula (IB), having a molecular weight of 557.5 and identified in table 2 below.

Example B 59

20 A mixture of chloro-1 dimethylamino-2 ethane (0.0044 mol) and NaHCO_3 (0.0087 mol) in DMF (10 ml) was stirred at RT for 30 minutes. Intermediate (13) (0.0050 mol) was added portionwise. The mixture was stirred at 70°C overnight, cooled, poured out onto water and neutralized with HCl 3N. The precipitate was filtered, washed with H_2O and
25 taken up in CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.4 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 94/6; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.58 g compound 59 of formula (IB), having a molecular weight of 574.5 and identified in table 2 below.

Example B 60

30 A mixture of 1-chloroethyl ethylcarbonate (0.0065 mol), intermediate (13) (0.0050

299

mol), NaHCO_3 (0.0050 mol) and potassium iodide (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then cooled and poured out into ice water. The precipitate was filtered off, washed with a diluted solution of HCl, washed with water, centrifugated and taken up in EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (3.3 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2 ; 70-200 μm). The desired fractions were collected and the solvent was evaporated. The residue (0.7 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.34 g compound 60 of formula (IB), having a molecular weight of 619.5 and identified in table 2 below.

Example B 61

A mixture of ethyl bromoacetate (0.0040 mol) in DMF (2 ml) was stirred at RT. A solution of intermediate (13)(0.0040 mol) and NaHCO_3 (0.0040 mol) in DMF (8 ml) was added. The mixture was stirred at 70°C for 2 hours, cooled, poured out into ice water and acidified with HCl 3N. The precipitate was filtered off, washed with water and taken up in EtOAc. The organic layer was separated, washed with water, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.2 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from diethylether. The precipitate was filtered off and dried, yielding 0.98 g compound 61 of formula (IB), having a molecular weight of 589.5 and identified in table 2 below.

Example B 62

A mixture of bromo-1 phenyl-3 propane (0.0065 mol), intermediate (13)(0.0050 mol), NaHCO_3 (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, then poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with a diluted solution of HCl, washed with water, dried (MgSO_4), filtered and the solvent was evaporated. The residue (3.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2 ; 70-200 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from diethylether/DIPE.

The precipitate was filtered off and dried, yielding 0.85 g compound 62 of formula (IB), having a molecular weight of 621.5 and identified in table 2 below.

Example B 63

5

A mixture of 2-(chloromethyl)benzimidazole (0.0044 mol) in DMF (5 ml) was added dropwise at RT to a mixture of intermediate (13)(0.0044 mol) and NaHCO₃ (0.0044 mol) in DMF (5 ml). The mixture was stirred at 70°C for 15 hours, cooled and poured out on ice. The precipitate was filtered off, washed with water several times,
10 centrifuged off and taken up in EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue (0.9 g) was crystallized from diethylether. The precipitate was filtered off and dried, yielding
15 0.4 g compound 63 of formula (IB), having a molecular weight of 633.5 and identified in table 2 below.

Example B 64

20 A mixture of cyclobutyl bromomethane (0.0040 mol) in DMF (2 ml) was added at RT to a mixture of intermediate (13)(0.0040 mol) and NaHCO₃ (0.0040 mol) in DMF (8 ml). The mixture was stirred at 70°C overnight, then cooled, poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.1 g) was purified by
25 column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.25/0.75; 15-40 µm, CH₃CN/NH₄Ac 75/25; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.9 g) was crystallized from diethylether. The precipitate was filtered off and dried, yielding 0.44 g compound 64 of formula (IB), having a molecular weight of 571.5 and identified in table 2 below.

30

Example B 65

A mixture of bromo-3 propanol-1 (0.0050 mol), intermediate (13)(0.0046 mol),

NaHCO₃ (0.0046 mol) in DMF (10 ml) was stirred at 70°C for 6 hours, then cooled and poured out into ice water. The precipitate was filtered, washed with a diluted solution of HCl and dried. The residue was taken up in CH₂Cl₂. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.6 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5; 15-40 μm). The desired fractions were collected and the solvent was evaporated. The residue (0.8 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.55 g compound 65 of formula (IB), having a molecular weight of 561.5 and identified in table 2 below.

10

Example B 66

A mixture of bromo-1 methyl-3 butene-2 (0.0040 mol) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mol) and NaHCO₃ (0.0040 mol) in DMF (8 ml). The mixture was stirred at 70°C for 20 hours, cooled, poured out into ice water, acidified with HCl 3N and then extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.0 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.5/0.5; 70-200 μm). The desired fractions were collected and the solvent was evaporated. The residue (0.5 g) was purified again by column chromatography over silica gel (eluent: CH₃CN/0.5%NH₄Oac 70/30; 10 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.25 g of compound 66 of formula (IB), having a molecular weight of 571.5 and identified in table 2 below.

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Example B 67

A mixture of iodomethyl trimethylacetate (0.0119 mol), intermediate (13)(0.0040 mol) and NaHCO₃ (0.0050 mol) in DMF (20 ml) was stirred at 70°C for 12 hours, then poured out on ice and acidified with HCl 3N. The precipitate was filtered off and dried. The residue was taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.3 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 μm to CH₃COONH₄/CH₃CN 25/75; 10 μm). The pure fractions were collected and the solvent

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was evaporated, yielding 0.25 g compound 67 of formula (IB), having a molecular weight of 617.5 and identified in table 2 below.

Example B 68

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A mixture of N,N-diethyl bromoacetamide (0.0065 mol), intermediate (13) (0.0050 mol) and NaHCO₃ (0.0050 mol) in DMF (10 ml) was stirred at 70°C for 12 hours, cooled and poured out on ice. The precipitate was filtered, washed with water, centrifuged off and taken up in EtOAc. The organic layer was separated, washed with a diluted solution of HCl, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3.1 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15–40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.4 g) was crystallized from CH₃CN and diethylether. The precipitate was filtered off and dried, yielding 0.7 g compound 68 of formula (IB), having a molecular weight of 616.5 and identified in table 2 below.

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Example B 69

A mixture of 4-chloro-1,3-dioxolan-2-one (0.0031 mol), intermediate (13) (0.0024 mol), NaHCO₃ (0.0024 mol) and potassium iodide (0.0024 mol) in DMF (6 ml) was stirred at 70°C for 5 hours, poured out into ice water and acidified with HCl 3N. The precipitate was filtered off, washed with water and taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.8 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15–40 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.65 g compound 69 of formula (IB), having a molecular weight of 589.5 and identified in table 2 below.

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Example B 70

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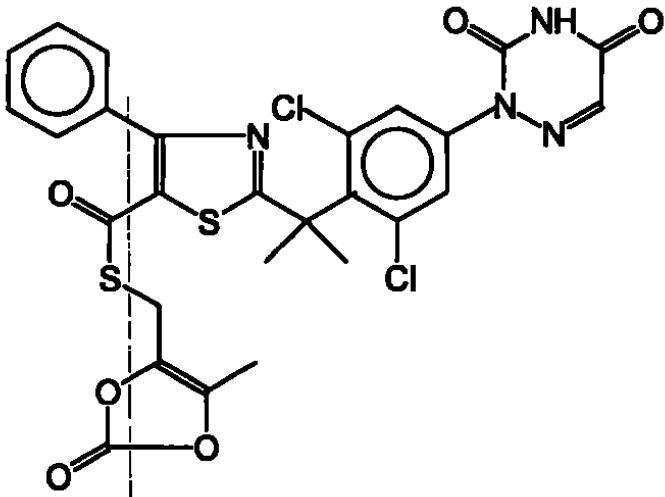
A mixture of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.0034 mol), intermediate (13) (0.0026 mol), NaHCO₃ (0.0026 mol) in DMF (6 ml) was stirred at 70°C for 12 hours, then poured out into ice water and acidified with HCl 3N. The precipitate was

289
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filtered, washed with water and taken up in CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (1.8 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2; 15-40 μm) then over Kromasil (eluent: $\text{CH}_3\text{CN}/\text{CH}_3\text{OH}$ 80/20; 3.5 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.28 g of compound 70 of formula (IB), having a molecular weight of 615.5 and identified in table 2 below.

Example B 71

A mixture of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.0046 mol), intermediate (14)(0.0035 mol), NaHCO_3 (0.0035 mol) in DMF (10 ml) was stirred at 70°C for 5 hours, poured out into ice water and acidified with HCl 3N. The precipitate was filtered, washed with water and taken up in CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1; 15-40 μm) then over Kromasil (eluent: $\text{CH}_3\text{CN}/\text{AcNH}_4$ 65/35; 10 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.36 g (33%) of compound 71, having a molecular weight of 631.5 and a melting point of 97°C and represented by the formula:



Example B 72

4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.0081 mol) was dissolved in DMF (20 ml). This solution was added dropwise to intermediate (10)(0.0077 mol) and NaHCO_3 (0.0081 mol) in DMF (30 ml) under nitrogen atmosphere. The reaction mixture was

stirred at 50°C for 3 hours, poured out into water (+ NaCl) and extracted three times with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by high performance liquid chromatography over silica gel (eluent: CH₂Cl₂/CH₃CN). The desired fractions were collected and the solvent was evaporated, yielding 0.86 g of an oily fraction which was stirred in hexane/EtOAc (1:1) until a white precipitate was formed. This precipitate was filtered off, washed with DIPE and dried overnight, yielding 0.58 g of compound 72, having a molecular weight of 629.5 and a melting point of 149°C and represented by the formula:

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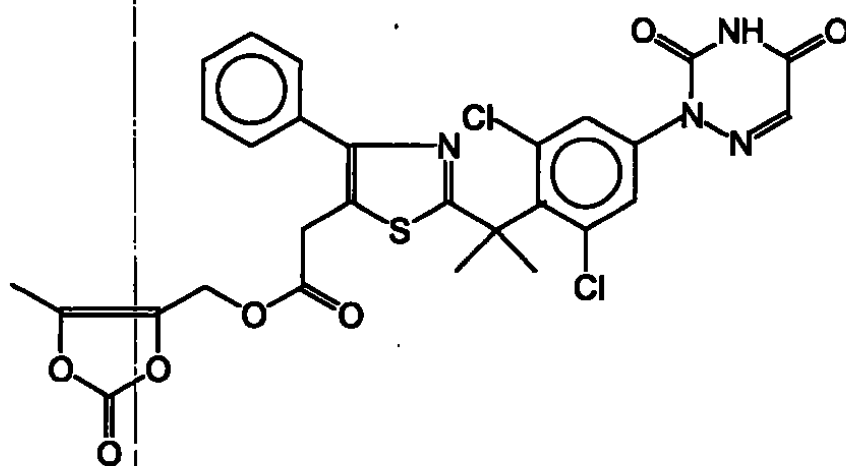
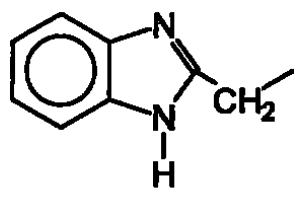
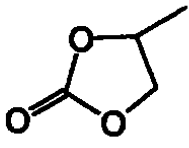
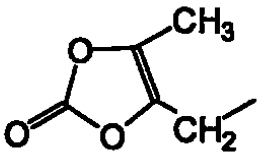


TABLE 2

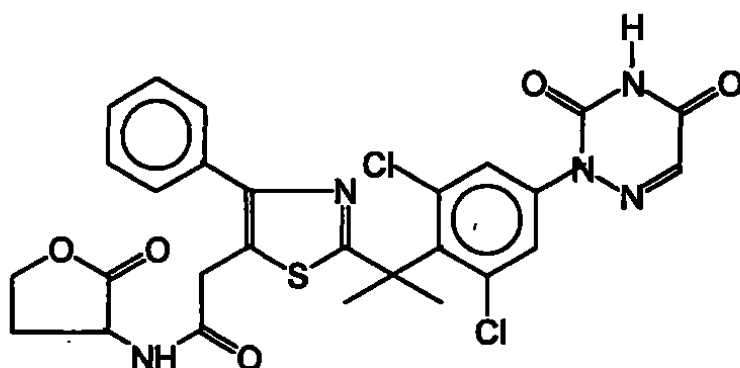
COMPOUND NO.	R ¹⁴	M.P. (°C)	Y (%)
54		182	53
55	Phenyl-2 ethyl	146	20
56	Phenylmethyl	167	30
57	Tert-butyl acetyl	165	17
58	Cyclopropylmethyl	100	13
59	dimethylaminoethyl	204	22
60		163	11

290
J

COMPOUND NUMBER	R ¹⁴	M.P. °C	Y(%)
61	ethylacetyl	198	
62	Phenyl-3 propyl	165	27
63		172	14
64	cyclobutylmethyl	80	33
65	Hydroxy-3 propyl	85	31
66	Methyl-3-butene-2-yl	90	11
67	trimethylacetyl	80	10
68	diethylacetamido	157	
69		90	36
70		102	14

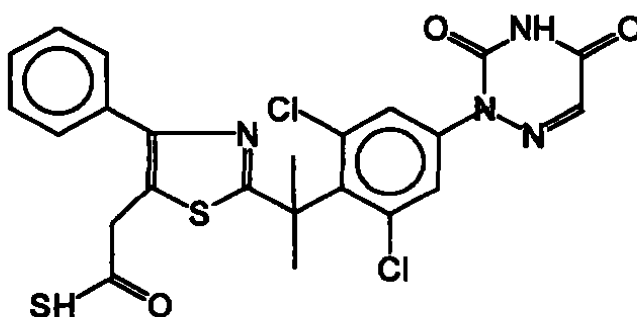
Example B 73

A mixture of intermediate (10) (0.00387 mol) and 1,1'-carbonylbis-1H-imidazole
 5 (0.0058 mol) in dichloromethane (40ml) was stirred at RT for 90 minutes, then
 (0.0058 mol) was added. The mixture was stirred at RT overnight, diluted with CH₂Cl₂
 and washed twice with an aqueous solution of NaCl. The organic layer was separated,
 dried (MgSO₄), filtered and the solvent was evaporated. The residue was filtered over
 silica gel (eluent: CH₂Cl₂/EtOAc 50/50). The product fractions were collected and the
 10 solvent was evaporated. The residue was crystallized from EtOAc. The residue was
 stirred in DIPE, filtered off, washed and dried at 50°C under vacuum for two days,
 yielding 1.43g (62%) compound 73 having a molecular weight of 600.5 and represented
 by the formula



Examples B 74 and B 75

- 5 A mixture of intermediate (10)(0.0156 mol) and 1,1'-carbonylbis-1H-imidazole (0.0232 mol) in DMF(160ml) was stirred at RT for 3 hours, and then treated with an excess of hydrogen sulfide for 20 minutes at RT, then with nitrogen overnight. Half of this reaction mixture, containing 0.0078 mol of compound 74 represented by the formula

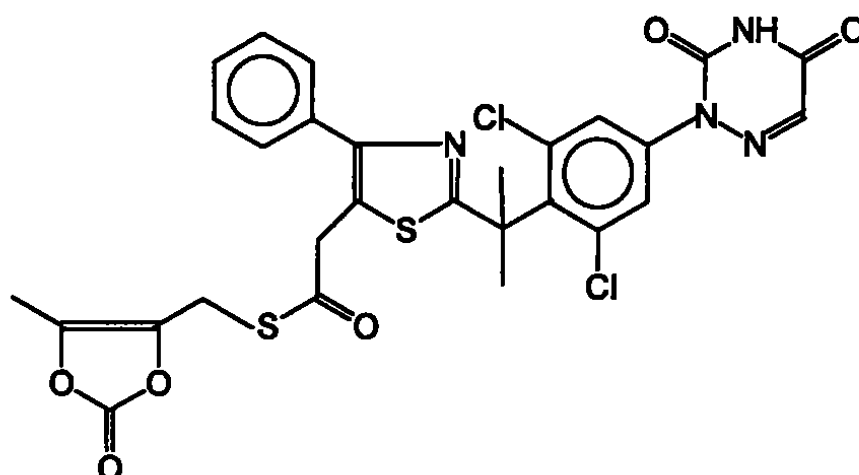


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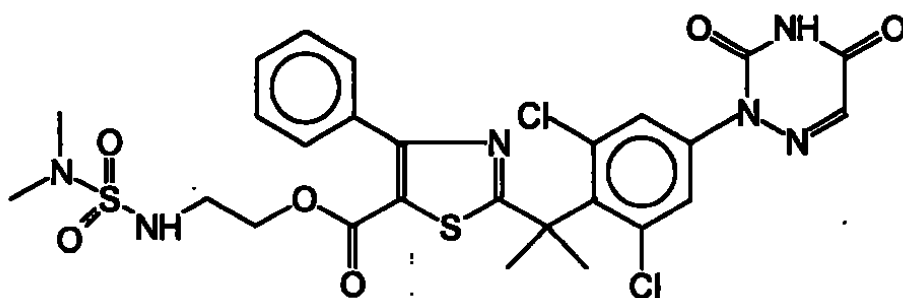
- in 80 ml DMF, was treated with a solution of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.013 mol) in DMF (20 ml). The reaction mixture was stirred for one hour, then poured out into water and extracted twice with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified over
15 silica gel on a glass filter (eluent: CH₂Cl₂/EtOAc 92.5/7.5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried under vacuum for one hour, yielding 2.68 g (54%) compound 75 represented by the formula

791
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61

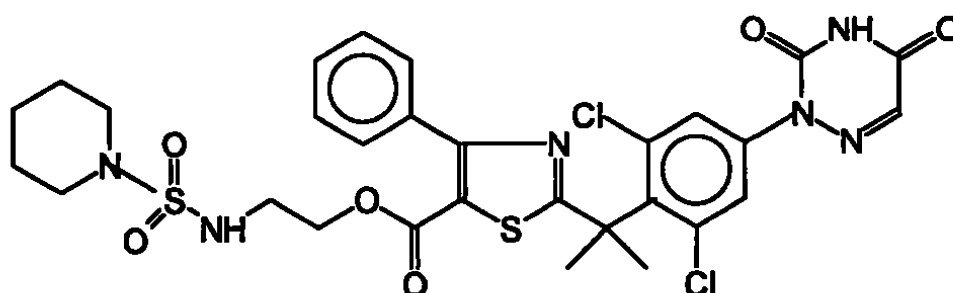
**Example B 76**

1,1'-carbonylbis-1H-imidazole (0.0017 mol) was added to a mixture of intermediate (13) (0.0014 mol) in DMF (6 ml). The mixture was stirred at 40°C for one hour. A solution of N,N-dimethyl ethanolaminesulfonamide (0.0028 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0014 mol) in DMF (3 ml) was added. The mixture was stirred at 40°C for 3 hours, then brought to RT, poured out into water, acidified with HCl 3N, filtered and washed with water. The precipitate was filtered off and dried. The residue was taken up in diethyl ether. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether/CH₃CN/DIPE, yielding 0.77 g (65%) of compound 76 having a molecular weight of 653.5 g, a melting point of 150°C and being represented by the formula

**Example B 77**

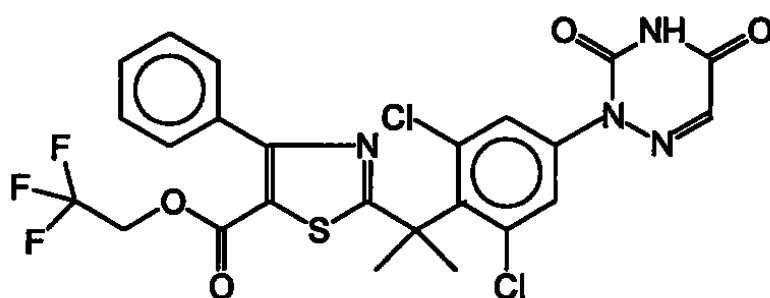
1,1'-carbonylbis-1H-imidazole (0.0013 mol) was added at RT to a mixture of

intermediate (13) (0.0010 mol) in DMF (4 ml). The mixture was stirred at 40°C for 45 minutes. A mixture of N-(2-hydroxyethyl)-1-piperidinesulfonamide (0.0019 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0010 mol) in DMF (2 ml) was added fastly. The mixture was stirred at 40°C for 90 minutes, then brought to RT, poured out into water and acidified with HCl 3N. The precipitate was filtered off and dried. The residue was taken up in CH₂Cl₂, then filtered and dried again and then purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue (0.34 g) was taken up in DIPE. The precipitate was filtered off and dried, yielding 0.18 g (57%) of compound 77 having a molecular weight of 693.5 g, a melting point of 126°C and being represented by the formula



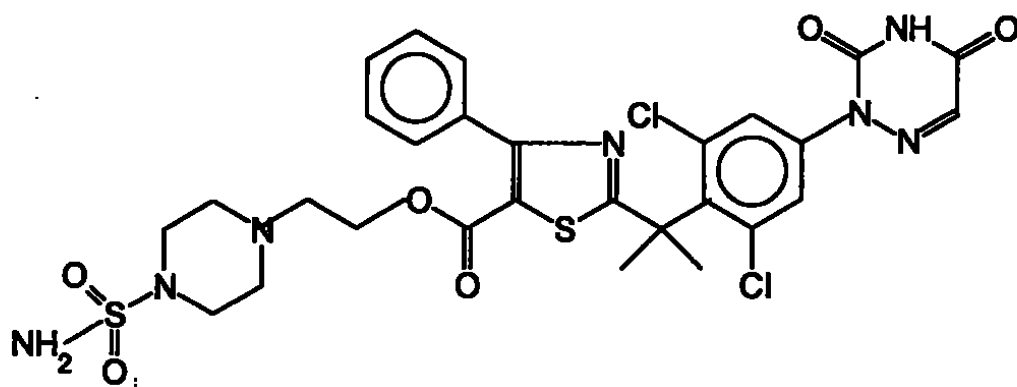
15 Example B 78

1,1'-carbonylbis-1H-imidazole (0.0030 mol) was added at RT to a mixture of intermediate (13) (0.0024 mol) in DMF (12 ml). The mixture was stirred at 40°C for one hour. A solution of 2,2,2-trifluoroethanol (0.0048 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0024 mol) in DMF (5 ml) was added. The mixture was stirred at 40°C for 2 hours, poured out on ice/HCl 3N, filtered and washed with water. The precipitate was taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether, then filtered off and dried, yielding 0.51 g (31%) of compound 78 having a molecular weight of 583.5 g, a melting point of 180°C and being represented by the formula



Example B 79

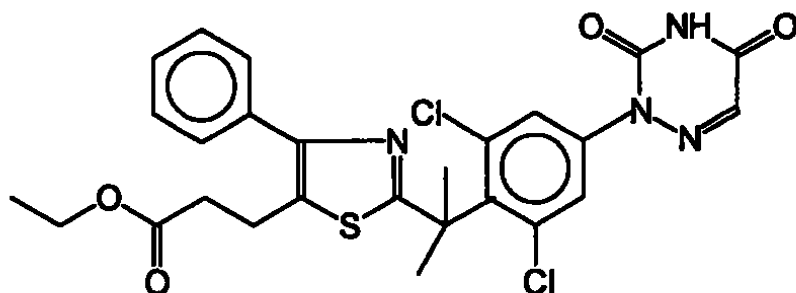
1,1'-carbonylbis-1H-imidazole (0.0050 mol) was added to a mixture of intermediate
5 (13) (0.0040 mol) in DMF (15 ml). The mixture was stirred at 40°C for one hour. A
solution of N-(2-hydroxyethyl)-N'-piperazinesulfonamide (0.0104 mol) and 1,8-
Diazabicyclo (5.4.0) undecene-7 (0.0040 mol) in DMF (10 ml) was added. The mixture
was stirred at 40°C for 2 hours, then brought to RT, poured out on ice water and
acidified with HCl 3N. The precipitate was filtered, washed with water and taken up in
10 CH₂Cl₂/CH₃OH. The organic layer was separated, dried (MgSO₄), filtered and the
solvent was evaporated. The residue (2.7 g) was purified by column chromatography
over silica gel (eluent: CH₂Cl₂/CH₃OH 96/4; 15-40 µm). The pure fractions were
collected and the solvent was evaporated, yielding 0.3 g (10%) of compound 79 having
a molecular weight of 694.5 g, a melting point of 133°C and being represented by the
15 formula



Example 80

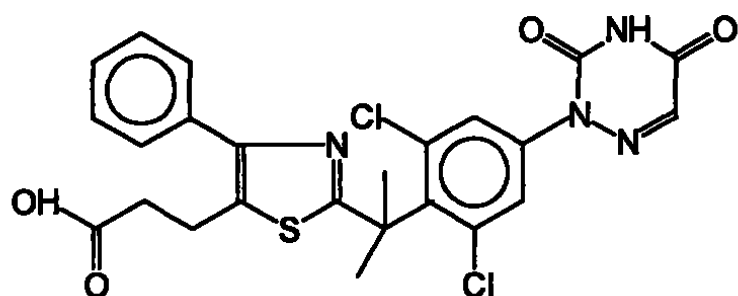
20 A mixture of intermediate (8) (0.0097 mol) and γ-bromo-δ-oxo-benzenepentanoic acid
ethyl ester (0.0126 mol) in ethanol (150 ml) was stirred and refluxed overnight. The
solvent was evaporated and the residue was taken up in methylene chloride. The organic

layer was separated, washed with a 10% solution of K_2CO_3 , then with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (5.7 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5; 15–40 μm). The pure fractions were collected and the solvent was evaporated, yielding 3.2 g (59 %) of compound 80 having a molecular weight of 559.5 g, a melting point of 155°C and being represented by the formula



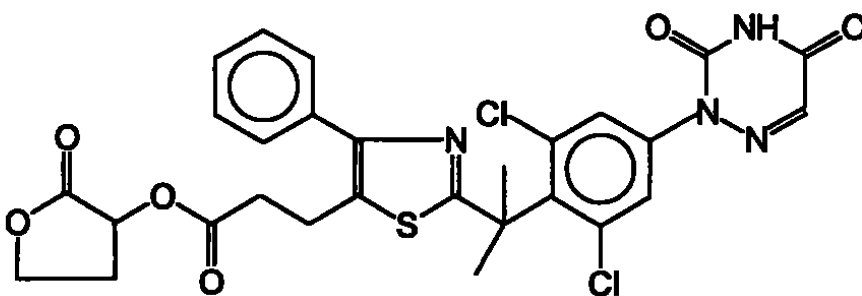
10 Example 81

A mixture of compound 80 (0.0032 mol) and sodium hydroxide (0.0096 mol) in methanol (20 ml) and THF (20 ml) was stirred at RT for 12 hours, poured out on ice, acidified with HCl 1N and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 1.7 g of a compound of the formula



which, after crystallization from diethyl ether, shows a melting point of 186°C. A mixture of α -bromo- γ -butyrolactone (0.0021 mol) in DMF (5 ml) was added dropwise at RT to a mixture of the compound obtained in the preceding step (0.0021 mol) and $NaHCO_3$ (0.0021 mol) in DMF (5 ml). The mixture was stirred at 70°C for 5 hours, poured out on ice, neutralized slowly with HCl (3N) and extracted with EtOAc and

washed with H₂O. The organic layer was separated, washed several times with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.1 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from diethylether and CH₃CN. The precipitate was filtered off and dried, yielding 0.25 g (19%) of compound 81 having a molecular weight of 615.5 g, a melting point of 190°C and being represented by the formula

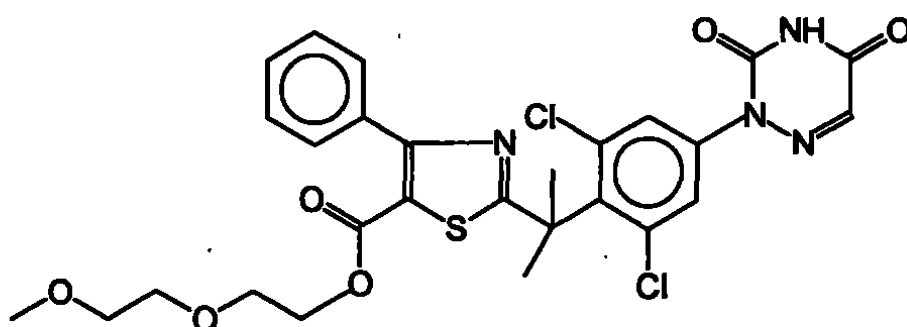


10 Example B 82

Intermediate (13) (0.0050 mol) was added to DMF (20 ml) under nitrogen flow.

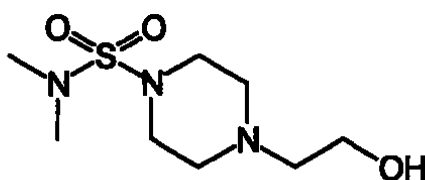
1,1'-carbonylbis-1H-imidazole (0.0062 mol) was added and the mixture was stirred at 40°C for one hour. Then 2-(2-methoxyethoxy) ethanol (0.0099 mol) and 1,8-

- 15 Diazabicyclo (5.4.0) undecene-7 (0.0050 mol) were added and the resulting mixture was stirred at 40°C for 12 hours, cooled and then diluted with diethyl ether. The organic layer was separated, washed with HCl 3N then with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 μm). The pure fractions were
- 20 collected and the solvent was evaporated. The residue (1.5 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.03 g (34%) of compound 82 having a molecular weight of 605.5 g, a melting point of 151°C and being represented by the formula



Example B 83

- 5 A mixture of N,N-dimethyl-1-piperazinesulfonamide (0.0423 mol) in methanol (100 ml) and methylene chloride (30 ml) was treated with an excess of gaseous ethylene oxide at 5°C for 90 minutes. The reaction mixture was stirred at RT for 3 hours. The solvent was evaporated, then co-evaporated with toluene. The residue was stirred overnight in 7N NH₃/CH₃OH and the solvent was evaporated, then co-evaporated with
- 10 toluene. The residue (10.3 g) was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 92.5/7.5). The desired fractions were collected and the solvent was evaporated, then co-evaporated with toluene, yielding 6.9 g (69 %) of a compound 83 represented by the formula



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which after crystallization from diethyl ether, shows a melting point of 186°C.

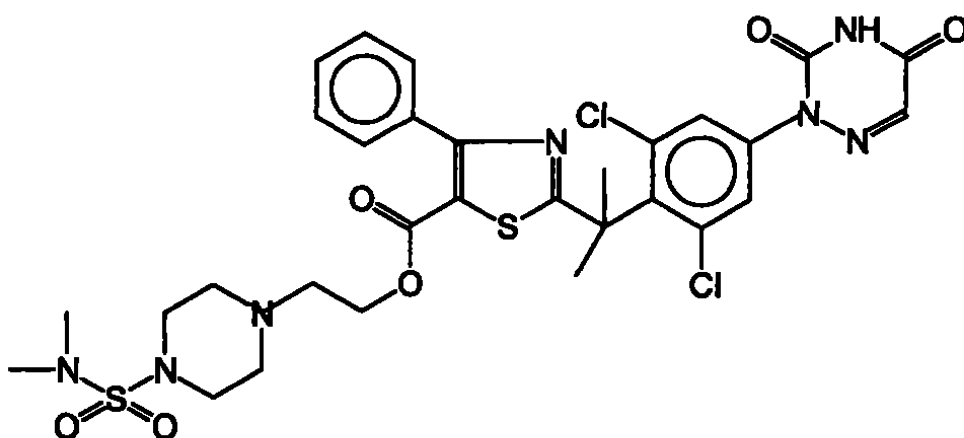
Example B 84

20

- Intermediate (13) (0.0036 mol) was added to DMF (15 ml) under nitrogen flow. 1,1'-carbonylbis-1H-imidazole (0.0045 mol) was added and the mixture was stirred at 40°C for one hour. Then a solution of compound 83 (0.0072 mol) and 1,8-Diazabicyclo (5.4.0) undecene-7 (0.0036 mol) was added over two minutes and the resulting mixture
- 25 was stirred at 40°C for 5 hours, brought to RT, poured out into water, filtered and taken

up in CH_2Cl_2 . The organic layer was separated, washed with water, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 97/3; 15–40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.3 g) was

5 crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried, yielding 1.0 g of compound 84 having a molecular weight of 722.7 g, a melting point of 220°C and being represented by the formula



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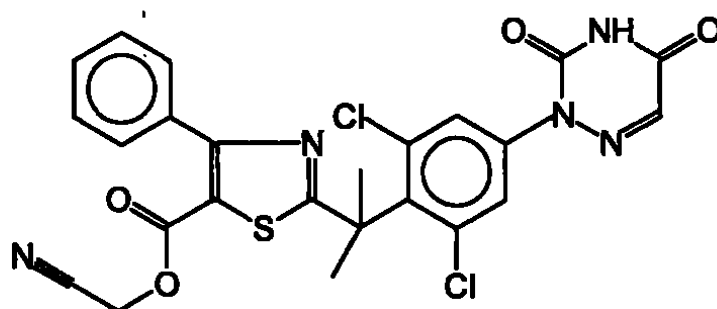
Example B 85

A mixture of bromoacetonitrile (0.0040 mol) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mol) and NaHCO_3 (0.0040 mol) in DMF (8 ml).

15 The mixture was stirred at 70°C overnight, cooled, poured out into ice water, acidified with HCl (3N) and then extracted with EtOAc. The organic layer was separated, washed with water, dried (MgSO_4), filtered and the solvent was evaporated. The residue (1.9 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99.25/0.75; 15–40 μm). The fractions were collected and, after evaporation of their

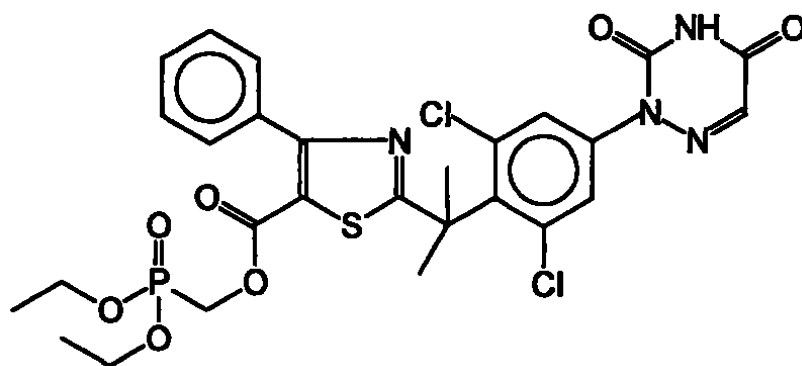
20 solvent, purified again by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99.25/0.75; 15–40 μm). The pure fractions were collected and the solvent evaporated, yielding 0.26 g (12%) of compound 85 having a molecular weight of 542.5 g and being represented by the formula

68



Example B 86

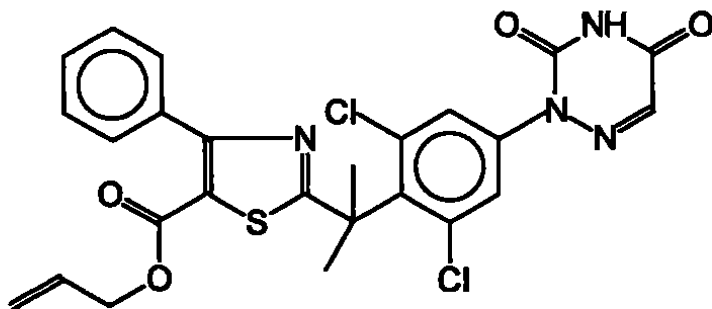
Intermediate (13) (0.0034 mol) was added under nitrogen flow to DMF (25 ml). 1,1'-
5 carbonylbis-1H-imidazole 0.0043 mol) was added and the mixture was stirred at 40°C
for one hour. (Hydroxymethyl) phosphonate diethyl ester (0.0068 mol) and 1,8-
Diazabicyclo (5.4.0) undecene-7 (0.0034 mol) were added and the mixture was stirred at
40°C for 5 hours, then brought to room temperature, poured out into water and acidified
with HCL 3N. The precipitate was filtered off and taken up in methylene chloride. The
10 organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent
was evaporated. The residue (3.0 g) was purified by column chromatography over silica
gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The fractions were collected and the
solvent was evaporated. The residue (1.4 g) was taken up in DIPE. The precipitate was
filtered off and dried, yielding 1.3 g of compound 86 having a molecular weight of
15 653.5 g, a melting point of 88°C and being represented by the formula



Example B 87

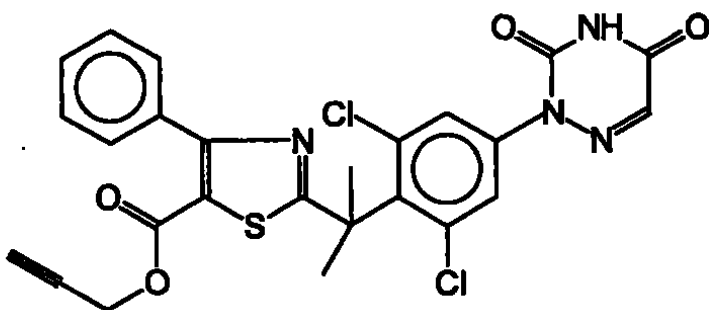
20 A mixture of bromo-3 propylene-1 (0.0040 mol) in DMF (2 ml) was added at RT to a
solution of intermediate (13) (0.0040 mol) and NaHCO₃ (0.0040 mol) in DMF (8 ml).
The mixture was stirred at 70°C overnight, poured out into ice water and extracted with

EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.5/0.5; 35-70 μm). The fractions were collected and the solvent evaporated. The residue (0.8 g) was crystallized from acetonitrile. The precipitate was filtered off and dried, yielding 0.31 g (15%) of compound 87 having a molecular weight of 543.5 g, a melting point of 172°C and being represented by the formula



Example B 88

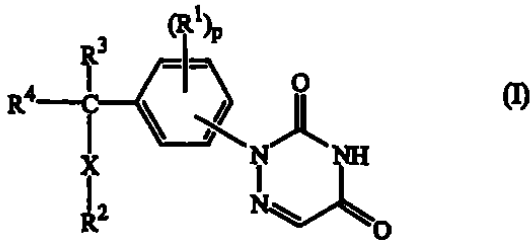
A mixture of bromoacetylene (0.0040 mol) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mol) and NaHCO₃ (0.0040 mol) in DMF (8 ml). The mixture was stirred at 70°C overnight, poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂; column: 70-200 μm). The desired fractions were collected and the solvent evaporated. The residue was purified again by column chromatography over silica gel (eluent: CH₃CN/NH₄Oac 68/32; column Kromasil C18 10 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.6 g) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.41 g of compound 88 having a molecular weight of 541.5 g, a melting point of 180°C and being represented by the formula



27. Dez. 1999

Claims

1. A compound having the formula



a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR⁵ or a direct bond or -*X*-R² taken together may represent cyano;

Y represents O, S, NR⁵, or S(O)₂;

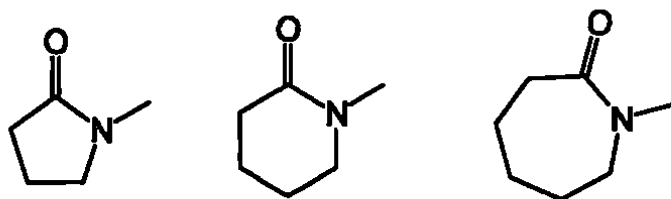
each R¹ independently represents C(=O)-Z-R¹⁴, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or C₁₋₄alkyl substituted with C(=O)-Z-R¹⁴, Het³, R⁶ or NR⁷R⁸; R² represents Het¹, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkyl or C₁₋₆alkyl substituted with one or two substituents selected from C(=O)-Z-R¹⁴, hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylsulfonyloxy, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if *X* is O, S or NR⁵, then R² may also represent aminothiocarbonyl, C₁₋₄alkylcarbonyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₄alkylthiocarbonyl optionally substituted with C(=O)-Z-R¹⁴, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl;

R³ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; R⁴ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; or R³ and R⁴ taken together form a C₂₋₆alkanediyl; R⁵ represents hydrogen or C₁₋₄alkyl;

each R⁶ independently represents C₁₋₆alkylsulfonyl, aminosulfonyl, piperidinylsulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl, phenylC₁₋₄alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C₁₋₄alkyl-*N*-piperidinylaminosulfonyl or mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkylsulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, arylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl,

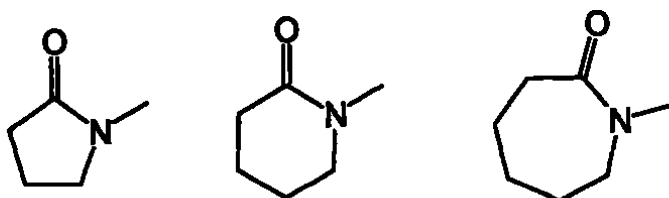
- 5 Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³, Het⁴ and R^6 ; or R^7 and R^8 taken together with the nitrogen atom to which they are attached form a radical of formula



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R^9 and R^{10} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl,

15 phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³, Het⁴ and R^6 ; or R^9 and R^{10} taken together with the nitrogen atom to which they are attached form a radical of formula

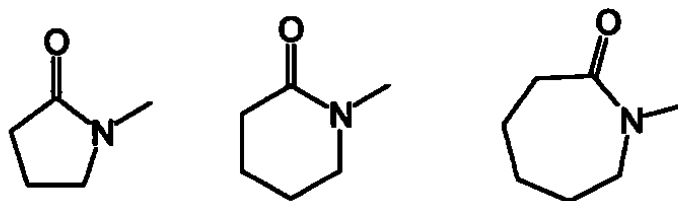


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- each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4} alkyloxy optionally substituted with C(=O)-Z- R^{14} , formyl,
- 25 trihalo C_{1-4} alkylsulfonyloxy, R^6 , NR^7R^8 , C(=O)NR¹⁵R¹⁶, -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , aryl, aryloxy, arylcarbonyl, C_{3-7} cycloalkyl optionally

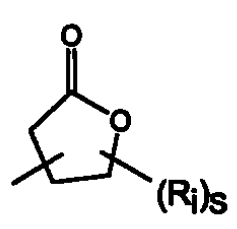
substituted with $C(=O)-Z-R^{14}$, C_{3-7} cycloalkyloxy optionally substituted with $C(=O)-Z-R^{14}$, phthalimide-2-yl, Het³ and $C(=O)Het^3$;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl- $C(=O)-Z-R^{14}$, $-C(=O)-Z-R^{14}$, $-Y-C_{1-4}$ alkanediyl- $C(=O)-Z-R^{14}$ and R^6 ; or R^{12} and R^{13} taken together with the nitrogen atom to which they are attached form a radical of formula

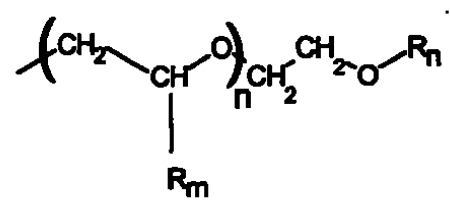


each R^{14} independently represents hydrogen, C_{1-20} acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C_{1-20} alkyl, C_{3-20} alkenyl optionally substituted with phenyl, C_{3-20} alkynyl, C_{3-7} cycloalkyl, polyhalo C_{1-20} alkyl, Het⁵, phenyl or C_{1-20} alkyl substituted with one or more substituents selected from hydroxy, $NR^{17}R^{18}$, phenyl, mono- or di-(C_{1-4} alkyl)amino, cyano, Het⁵, C_{1-4} alkyloxycarbonyl, phenyl C_{1-4} alkyloxycarbonyl and C_{3-7} cycloalkyl, or R^{14} represents a radical of formula

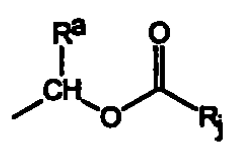
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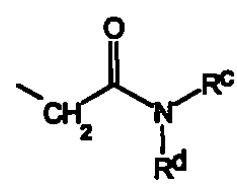
(a)



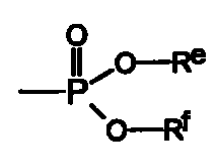
(b)



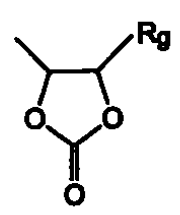
(c)



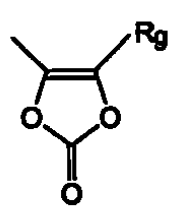
(d)



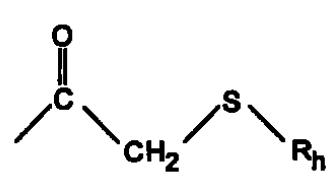
(e)



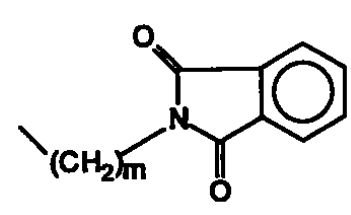
(h)



(i)

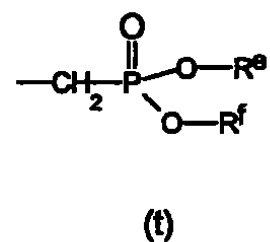
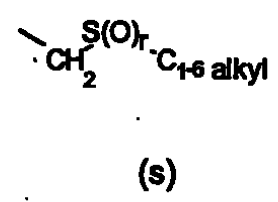
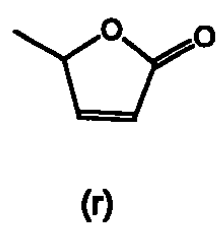
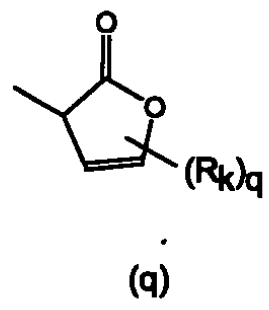
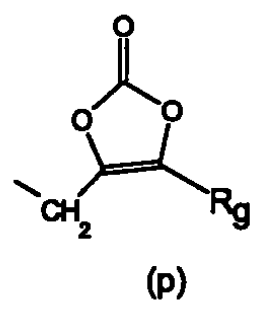
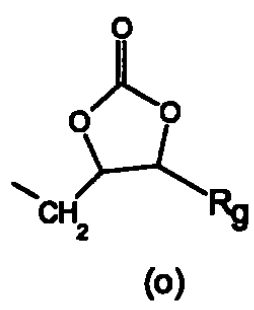
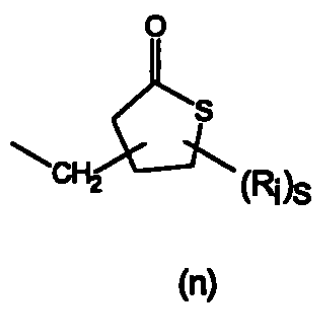
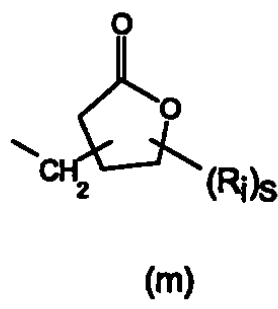
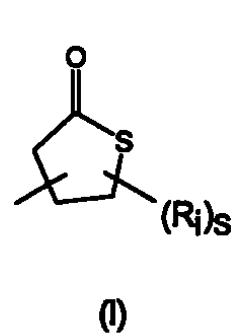


(j)



(k)

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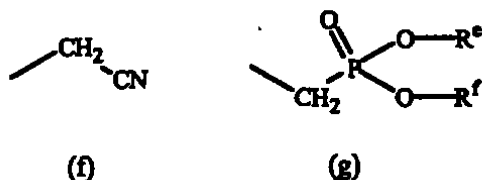


wherein m is 1 to 4, n is 0 to 5, q is 0 to 2, r is 0 to 2 and s is 0 to 4;
 R^a , R^b , R^c , R^d , R^e and R^f are each independently hydrogen, C_{1-6} alkyl, phenyl or C_{3-7} cycloalkyl; or
 R^e and R^f taken together may form $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-CH_2-$;
 R_p , R_h and R_i are each independently hydrogen or C_{1-4} alkyl;
 R_j is C_{1-4} alkyl;
 R_k is $-O-R_h$, C_{1-6} alkyl, phenyl or C_{3-7} cycloalkyl optionally substituted with C_{1-4} alkyloxy;

where R_m is hydrogen or C_{1-4} alkyloxy and R_n is hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, phenyl or phenyl C_{1-4} alkyl

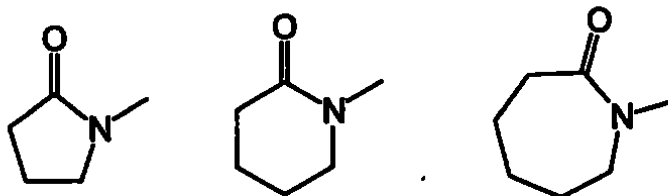
each Z independently represents O, S, NH, $-CH_2-O-$ or $-CH_2-S-$ whereby $-CH_2-$ is attached to the carbonyl group; or

-Z-R¹⁴ taken together form a radical of formula



R¹⁵ and R¹⁶ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, -C(=O)-Z-R¹⁴,
 5 arylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, aminocarbonylmethylene, mono- or di(C₁₋₄alkyl) aminocarbonylmethylene, Het³aminocarbonyl, Het³aminothiocarbonyl, pyridinylC₁₋₄alkyl, Het³ or R⁶; or R¹⁵ and R¹⁶ taken together with the nitrogen atom to which they are attached form a radical of formula

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R¹⁷ and R¹⁸ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, phenylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-Z-C₁₋₄alkyl, -C(=O)-Z-C₁₋₄alkyl, -Y-C₁₋₄alkanediyl-C(=O)-Z-C₁₋₄alkyl and R⁶;
 aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-Z-R¹⁴, R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³ or NR⁹R¹⁰;

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Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl,

- pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl,
- 5 isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het² and R¹¹;
- 10 Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl,
- 15 benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or
- 20 three substituents each independently selected from Het⁴, R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het⁴ and R¹¹;
- Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with,
- 25 where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹²R¹³, C(=O)-Z-R¹⁴, R⁶ and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, phenyl, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, R⁶ and NR¹²R¹³;
- 30 Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl;

Het⁵ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolanyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-
d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-
b]thiazolyl; wherein said heterocycles each independently may be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹⁷R¹⁸, C(=O)-Z-C₁₋₆alkyl, R⁶, sulfonamido and C₁₋₄alkyl substituted with one or two substituents
independently selected from hydroxy, C₁₋₄alkyloxy, phenyl, C(=O)-Z-C₁₋₆alkyl, -Y-C₁₋₄alkanediyl-C(=O)-Z-C₁₋₆alkyl, R⁶ and NR¹⁷R¹⁸;

provided however that

- R² is other than C₁₋₆alkyloxycarbonylC₁₋₆alkyl or aminocarbonyl; and
- R⁷, R⁸, R⁹ and R¹⁰ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, C(=O)-O-R¹⁹, C₁₋₄alkanediylC(=O)-O-R¹⁹ or -Y-C₁₋₄alkanediylC(=O)-O-R¹⁹; and
- R¹² and R¹³ are other than C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl or C₁₋₄alkylcarbonylcarbonyl; and
- R¹¹ is other than C(=O)-O-R¹⁹, Y-C₁₋₄alkanediyl - C(=O)-OR¹⁹, C(=O)NH₂, C(=O)NHC₁₋₄alkyl or C(=O)NHC₃₋₇cycloalkyl; and
- R¹⁵ and R¹⁶ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl or C₁₋₄alkyloxycarbonylcarbonyl; and
- aryl is other than phenyl substituted with C(=O)-O-R¹⁹, C(=O)NH₂, C(=O)NHC₁₋₄alkyl, C(=O)NHC₃₋₇cycloalkyl and/or with C₁₋₄alkyl substituted with C(=O)-O-R¹⁹ or Y-C₁₋₄alkanediyl - C(=O)-O-R¹⁴; and
- Het³ is other than a monocyclic heterocycle substituted with C(=O)-O-R¹⁹ and/or with C₁₋₄alkyl substituted with C(=O)-O-R¹⁹ and/or Y-C₁₋₄alkanediyl - (=O)-O-R¹⁹; and

- in each of the above proviso's R^{19} is defined as hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, aminocarbonylmethylene or mono- or di(C_{1-4} alkyl)aminocarbonylmethylene; and
- the said compound of formula (I) contains at least one $-C(=O)-Z-R^{14}$ moiety.

5 2. A compound according to claim 1 wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents.

10 3. A compound according to claims 1 or 2 wherein R^2 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2 , R^{11} and C_{1-4} alkyl optionally substituted with Het^2 or R^{11} .

15

4. A compound according to any of claims 1 to 3 wherein R^3 and R^4 are both methyl and $-X-R^2$ is Het^1 .

20

5. A compound according to any of claims 1 to 4 wherein p is 1 or 2 and each R^1 is chloro.

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6. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to any of claims 1 to 5.

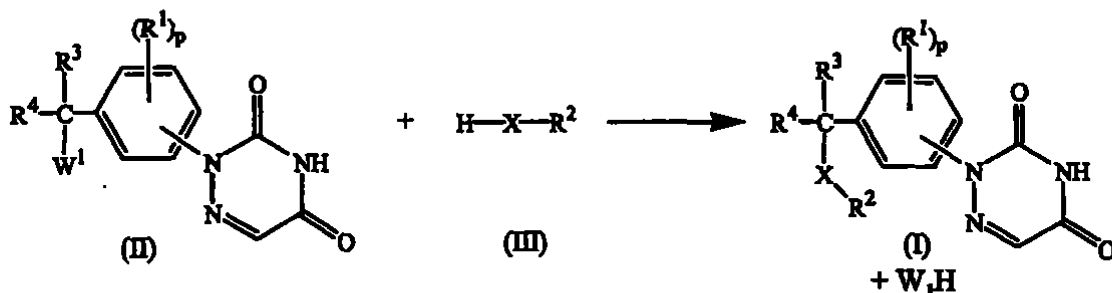
7. A process for preparing a composition as claimed in claim 6, , wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound according to any of claims 1 to 5.

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8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

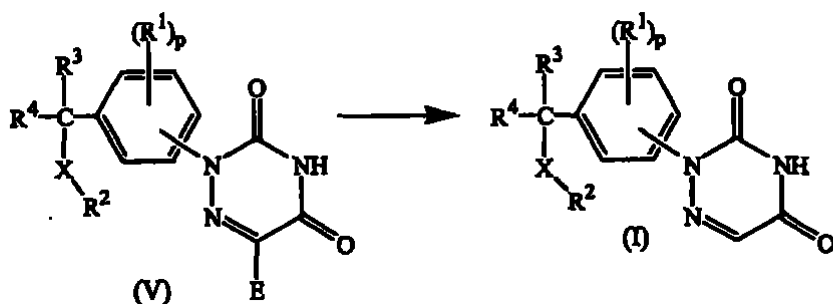
9. Use of a compound according to any of claims 1 to 5 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases.

10. A process for preparing a compound as claimed in claim 1, comprising the step of
 a) reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group with
 an
 5 appropriate reagent of formula (III) optionally in a reaction-inert solvent and
 optionally in the presence of a base at a temperature ranging between -70°C and
 reflux temperature;



wherein R^1 , R^2 , R^3 , R^4 , p and X are as defined in claim 1 or;

- 10 b) eliminating the group E of a triazinedione of formula (V)



wherein E is an appropriate electron attracting group and R^1 , R^2 , R^3 , R^4 , X and p are as defined in claim 1;

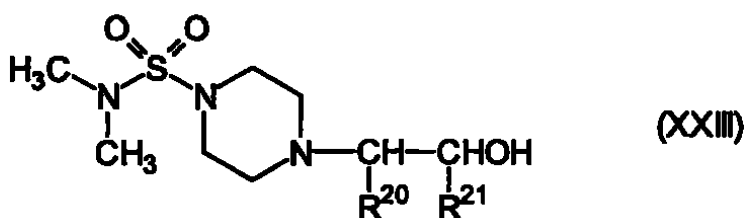
- and, if desired, converting compounds of formula (I) into each other following art-
 15 known transformations, and further, if desired, converting the compounds of formula
 (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid,
 or into a therapeutically active non-toxic base addition salt by treatment with a base, or
 conversely, converting the acid addition salt form into the free base by treatment with
 alkali, or converting the base addition salt into the free acid by treatment with acid; and
 20 also, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

11. A process of marking a receptor comprising the steps of
- a) radiolabelling a compound as defined in claim 1;
 - b) administering said radiolabelled compound to biological material,
 - c) detecting the emissions from the radiolabelled compound.

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12. A process of imaging an organ, characterized by, administering a sufficient amount of a radiolabelled compound of formula (I) in an appropriate composition, and detecting the emissions from the radioactive compound.

- 10 13. A compound of formula



wherein R^{20} and R^{21} are each independently selected from hydrogen or C_{1-20} alkyl or R^{20} and R^{21} taken together with the carbon atom to which they are attached form a cycloalkyl radical.

15

14. Use of the compound of claim 13 for preparing a compound of claim 1 wherein Het^5 represents a sulfonamido substituted piperazine.

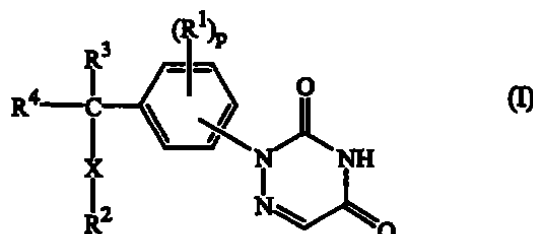
ABSTRACT

27. Dez. 1999

NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

5

The present invention is concerned with the compounds of formula



the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein *p* is 0 to 4; *X* is O, S, NR⁵ or a direct bond; *Y* is O, S, NR⁵ or S(O)₂; R¹ independently is C(=O)-Z-R¹⁴, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or substituted C₁₋₄alkyl; R² is Het¹, optionally substituted C₃₋₇cycloalkyl or C₁₋₆alkyl and if *X* is O, S or NR⁵, then R² may also represent C(=O)-Z-R¹⁴, aminothiocarbonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; R³ and R⁴ independently are hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl or R³ and R⁴ together form a C₂₋₆alkanediyl; R⁵ is hydrogen or C₁₋₄alkyl; R⁷ and R⁸ are independently hydrogen, optionally substituted C₁₋₄alkyl, aryl, a carbonyl containing moiety, C₃₋₇cycloalkyl, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴ or Het³; R⁶ is a sulphonyl; R¹⁴ is hydrogen, C₁₋₂₀alkyl, C₃₋₇cycloalkyl, C₁₋₂₀ acyl or another radical; Z is O, S, NH, -CH₂O- or -CH₂S- whereby -CH₂- is attached to the carbonyl group; aryl is optionally substituted phenyl; Het¹, Het², Het³ and Het⁴ are optionally substituted heterocycles, provided that the said compounds contain at least one -C(=O)-Z-R₁₄ moiety; to processes for their preparation and pharmaceutical compositions comprising them. It further relates to their use as a medicine.

25

303-
Janssen
JAB 1520
316

TRADUCCION OFICIAL No. 139/00 DE UN DOCUMENTO ESCRITO EN FRANCES, EL CUAL PARA SU IDENTIFICACION SE SELLA CON EL SELLO DEL TRADUCTOR. ESTA ES UNA TRADUCCION OFICIAL EFECTUADA EL DIA 01 DE SEPTIEMBRE DEL AÑO 2000 POR JEAN-JACQUES TURPIN, C.E.: 193849 DE BOGOTA, TRADUCTOR OFICIAL SEGUN RESOLUCION No. 2680/91 DEL 19 DE DICIEMBRE DE 1991, EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE COLOMBIA.

Autenticaciones que se hallan a continuación de un documento de traspaso conferido en inglés y en español por Jean Fernand Armand Lacrampe y Jérôme Michel Claude Fortin, domiciliados en Janssen Cilag S.A, 1, rue Camilles Desmoulins TSA 91003, 92787 Issy-les-Moulineaux, Cedex 9 Francia, quienes declaran ser los únicos y verdaderos inventores de "inhibidores il-5 no-esteroidales, procedimientos para su preparación y composiciones farmacéuticas que los contienen". Declaran asimismo ceder y transferir sin reserva ni limitación a la sociedad Janssen Cilag S.A., sociedad organizada y existente de acuerdo con las leyes de Francia, domiciliada en 1, rue Camilles Desmoulins TSA 91003, 92787 Issy-les-Moulineaux, Cedex 9, Francia, todos los derechos inherentes a dicha invención, y que la sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia. Firma ilegible de Jean Fernand Armand Lacrampe y Jérôme Michel Claude Fortin.

Legalización de la firma de los Señores Jean Fernand Armand Lacrampe y Jérôme Michel Claude Fortin por Philippe Bougeard, Notario asociado en Le Mesnil-Esnard (Seine-Maritime). Firma ilegible del Notario.

Sello: Philippe Bougeard - Notario asociado en Le Mesnil-Esnard - República francesa.

Traducción Oficial No. 139/00
JEAN - JACQUES H. TURPIN
Traductor e Interpreté Oficial
FRANCOIS - ESPANOL
Res. Minjusticia No. 2680/91

304 317

Certificación notarial de presentación personal y legalización de firma de los Señores Jean Fernand Armand Lacrampe y Jérôme Michel Claude Fortin, con fecha del 10 de Julio del año 2000, por parte del Señor Jean-Marie VAUCHELLE, Notario Asociado en Mesnil-Esnard (Seine-Maritime). Firma ilegible del Notario.

Sello: Jean-Marie Vauchelle – Notario asociado – Le Mesnil-Esnard (Seine-Maritime) República francesa.

Sello en tinta del Ministerio de Relaciones Exteriores. Hace constar que la presente certificación de firma se ha efectuado de conformidad con la ley francesa. Por el Ministro y por delegación. Firmado (ilegible): Dominique Lefay.

Otro sello del Ministerio de Relaciones Exteriores del 16 de Agosto del año 2000, bajo el No.065324 - República Francesa 010.

EN ESPAÑOL. Legalización de la firma de Dominique Lefay por el Consulado General de Colombia en Paris, el 16 de Agosto del año 2000 bajo el No. 3238. Pagado el impuesto de timbre por valor de veintidós dólares (U.S.\$22.00): Sello del Consulado General de Colombia en Paris. Sello y firma del Cónsul General de Colombia, Alejandro Borda Rojas.

Legalización de la firma de Alejandro Borda Rojas por el Ministerio de Relaciones Exteriores en Bogotá No. 425811 del 30 de Agosto del año 2000. Firma y sello del Jefe de legalizaciones.

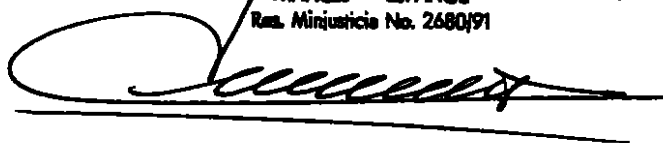
Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para confrontación y a la cual me remito.

Traducción oficial No. 139/00.

Traductor: Jean-Jacques Turpin.

Santafé de Bogotá, D.C., 01 de Septiembre del año 2000.

Traducción Oficial No. 139/00
JEAN - JACQUES H. TURPIN
Traductor e Interpreté Oficial
FRANCOIS - ESPANOL
Res. Minjusticia No. 2680/91



INSTRUMENTOS
EXTERIORES

525965

CUYAFIRMA AFIRME EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

POSESIÓN
RESPONSABILIDAD

210 SEP -4 10 10

JEFE DE LEGALIZACIONES
SANTANA DE CUCUTA D

ASSIGNMENT

The undersigned,
Jean Fernand Armand Lacrampe
Jérôme Michel Claude Fortin

TRASPASO 065324

MINISTRE DES AFFAIRES
ÉTRANGÈRES
16 AOUT 2000
CÔNUL DE COLOMBIE
Dominique LEFAY

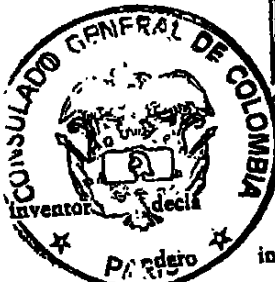
Janssen 000100
REPOUQUE
010
FRANCAISE

domiciled in

c/o Janssen Cilag S.A., 1, rue Camille Desmoulins

TSA 91003, 92787 Issy-les-Moulineaux, Cedex 9, France

PAGADO IMPUESTO DE TIMBRE
VALOR US\$ 22



ALEJANDRO BORDA ROJAS
Cónsul General de Colombia

bajo juramento ser único y verda-

hereby state under oath to be the sole and true
inventor of

NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

INHIBIDORES I L-5 NO ESTEROIDALES, PROCEDIMIENTOS INTERMEDIARIOS PARA SU PREPARACION Y COMPOSICIONES FARMACEUTICAS QUE COMPRENDEN DICHOS INHIBIDORES

MINISTERIO DE RELACIONES
EXTERIORES
11-25-81-11
CUBA
DOCUMENTO DESEMPENAR
LAS FUNCIONES INDICADAS

or limitation, in favor of
Janssen Cilag S.A.

assign, without reservations

Declaramos asimismo que cedemos y
transferimos sin reserva ni limitación, a favor de la
sociedad Janssen Cilag S. A.

a corporation organized and existing under the laws of
France

organizada y existente de conformidad con las leyes de
Francia

domiciled in 1, rue Camille Desmoulins, TSA 91003
92787 Issy-les-Moulineaux, Cedex 9, France

domiciliada en

LE MINISTRE DES AFFAIRES ÉTRANGÈRES
Constata que la présente certification de signature
a été effectuée conformément à la loi française
Pour le Ministre et par délégation



Dominique LEFAY

all rights inherent to said invention, and that the above
mentioned corporation hereby is enabled to apply, in its
name, for the corresponding patent in the Republic of
Colombia.

Jean F. A. Lacrampe

todos los derechos inherentes a dicha invención, y que la
citada sociedad queda facultada para solicitar y obtener
la patente correspondiente en la República de Colombia.
Jérôme M. CaFortin
LACRAMPE & FORTIN



CERTIFICADO NOTARIAL

(INDIVIDUO)

NOTARIAL CERTIFICATE

(INDIVIDUAL)

A los 13 días del mes de July,
de 19 1990, comparecí personalmente ante mí,
Notario Público,

On this 13 day of July,
19 1990 personally appeared before me, a Notary Public,

a quien doy fé de conocer y me consta que
la persona descrita y firmante
del documento que precede, declarando ante mí que otor-
ga el mismo para los fines y propósitos que en él se
expresan.

to me known and known to me to be the person
described in and who executed the foregoing document,
and duly acknowledged to me that
executed the same for the uses and purposes
therein expressed.

NOTARY PUBLIC (Notario Público)

Me Jean-Marie VAUCHELLE, Notaire associé
au MESNIL-ESNARD (Seine-Maritime) certifie
sincère et véritable la signature apposée ci-
contre, comme émanant de M. LACRAMPE & FORTIN

Traducción Oficial No. 139/00
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Min. Justicia No. 2680/91



CERTIFICADO NOTARIAL

(INDIVIDUO)

NOTARIAL CERTIFICATE

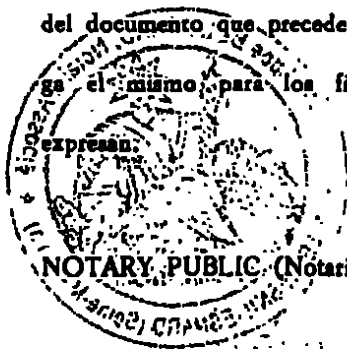
(INDIVIDUAL)

A los 10 días del mes de July,
de 19 1990, comparecí personalmente ante mí,
Notario Público,

On this 10th day of July,
1990 personally appeared before me, a Notary Public,

a quien doy fé de conocer y me consta que
la persona descrita y firmante
del documento que precede, declarando ante mí que otor-
ga el mismo para los fines y propósitos que en él se
expresan.

to me known, and known to me to be the person
described in and who executed the foregoing document,
and duly acknowledged to me that
executed the same for the uses and purposes
therein expressed.



NOTARY PUBLIC (Notario Público)

306 Janssen
LAB 1520-02
319
305

TRADUCCION OFICIAL No. 140/00 DE UN DOCUMENTO ESCRITO EN FRANCES, EL CUAL PARA SU IDENTIFICACION SE SELLA CON EL SELLO DEL TRADUCTOR. ESTA ES UNA TRADUCCION OFICIAL EFECTUADA EL DIA 01 DE SEPTIEMBRE DEL AÑO 2000 POR JEAN-JACQUES TURPIN, C.E.: 193849 DE BOGOTA, TRADUCTOR OFICIAL SEGUN RESOLUCION No. 2680/91 DEL 19 DE DICIEMBRE DE 1991, EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE COLOMBIA.

Autenticaciones que se hallan a continuación de un documento de traspaso conferido en inglés y en español por Janssen Cilag S.A., domiciliada en 1, rue Camilles Desmoulins TSA 91003, 92787 Issy-les-Moulineaux, Cedex 9 Francia, quien declara ser la única y verdadera inventora de "inhibidores il-5 no-esteroidales, procedimientos para su preparación y composiciones farmacéuticas que los contienen". Declaran asimismo ceder y transferir sin reserva ni limitación a la sociedad Janssen Pharmaceutica N.V., sociedad organizada y existente de acuerdo con las leyes de Bélgica, domiciliada en Turnhoutseweg 30,B-2340 Beerse, Bélgica, todos los derechos inherentes a dicha invención, y que la sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia. Firma ilegible de Frédéric Champavère, Director General.

Legalización de la firma del Señor Frédéric Champavère por Jean-Philippe Bougeard, Notario asociado en Le Mesnil-Esnard (Seine-Maritime). Firma ilegible del Notario.

Sello: Philippe Bougeard - Notario asociado en Le Mesnil-Esnard - República francesa.

Certificación notarial de presentación personal y legalización de firma de Frédéric Champavère, con fecha del 10 de Julio del año 2000, por parte del Señor Jean-

Traducción Oficial No. 140/00
JEAN - JACQUES H. TURPIN
Traductor e Interpreté Oficial
FRANCOIS - ESPANOL
Res. Minjusticia No. 2680/91

Marie VAUCHELLE, Notario Asociado en Mesnil-Esnard (Seine-Maritime). Firma ilegible del Notario.

Sello: Jean-Marie Vauchelle – Notario asociado – Le Mesnil-Esnard (Seine-Maritime)
República francesa.

Sello en tinta del Ministerio de Relaciones Exteriores. Hace constar que la presente certificación de firma se ha efectuado de conformidad con la ley francesa. Por el Ministro y por delegación. Firmado (ilegible): Dominique Lefay.

Otro sello del Ministerio de Relaciones Exteriores del 16 de Agosto del año 2000, bajo el No.065323 - República Francesa 010.

ANEXO

Certificación, por parte del Consulado General de Colombia en Paris, Francia, No.3237, del 16 de Agosto del año 2000, de la firma de Dominique Lefay quien desempeña las funciones de Secretaría Administrativa de la Dirección de los Franceses en el Exterior y de los Extranjeros en Francia del Ministerio de Asuntos Exteriores de Francia. Además, certifica la existencia y representación de la compañía JANSSEN CILAG S.A. y certifica que el Señor Frédéric Champavère desempeña el cargo de Presidente de dicha compañía y es el representante legal de la misma. Sello del Consulado General de Colombia en Paris. Pagado el impuesto de timbre por valor de veintidós dólares (US\$22.00) Sello y firma del Cónsul General de Colombia, Alejandro Borda Rojas.

Traducción Oficial No. 140/00
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCOIS - ESPANOL
Res. Minjusticia No. 2680/91

308.321

Legalización de la firma de Alejandro Borda Rojas por el Ministerio de Relaciones Exteriores en Bogotá No. 425812 del 30 de Agosto del año 2000. Firma y sello del Jefe de legalizaciones.

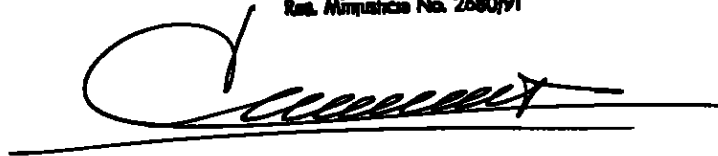
Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para confrontación y a la cual me remito.

Traducción oficial No. 140/00.

Traductor: Jean-Jacques Turpin.

Santafé de Bogotá, D.C., 01 de Septiembre del año 2000.

Traducción Oficial No. 140/00
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCOIS - ESPANOL
Res. Minjusticia No. 2680/91



PLANTILLA DE FOLIOS
EXHIBIDOS

523600

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPA
LAS FUNCIONES INDICADAS

RESPONSABLE DEL

7/11 SET - 4 F 1102

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D C

ASSIGNMENT

The undersigned,

Janssen Cilag S.A.



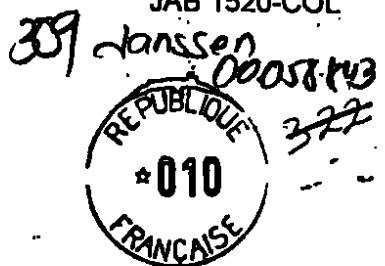
TRASPASO

065322

MINISTRE DES AFFAIRES
ÉTRANGÈRES

16 AOU 2000

JOSE LL B3237 CAMACHO & C
JAB 1520-COL



domiciled in

1, rue Camille Desmoulins
TSA 91003, 92787 Issy-les-Moulineaux, Cedex 9, France

domiciliado en

1, rue Camille Desmoulins
TSA 91003, 92787 Issy-les Moulineaux,
Cedex 9, Francia

hereby state under oath to be the sole and true inventor of
declaro bajo juramento ser único y verda-
dero inventor de

NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION AND
PHARMACEUTICAL COMPOSITIONS COMPRISING THEM
INHIBIDORES I L-5 NO ESTEROIDALES, PROCEDIMIENTO E INTERMEDIARIOS PARA SU
PREPARACION Y COMPOSICIONES FARMACEUTICAS QUE COMPRENDEN DICHOS INHIBIDORES.

state as well that assign, without reservations
or limitation, in favor of
Janssen Pharmaceutica N.V.

Declaro asimismo que cedo y
transfiero sin reserva ni limitación, a favor de la
sociedad Janssen Pharmaceutica N.V.

a corporation organized and existing under the laws of
Belgium

organizada y existente de conformidad con las leyes de
Belgica
LE MINISTRE DES AFFAIRES ÉTRANGÈRES
Constata que la présente certification de signature
a été effectuée conformément à la loi française
Pour le Ministre et par délégation

domiciled in
Turnhoutseweg 30, B-2340 Beerse, Belgium

domiciliada en
Turnhoutseweg 30, B-2340 Beerse,
Belgica



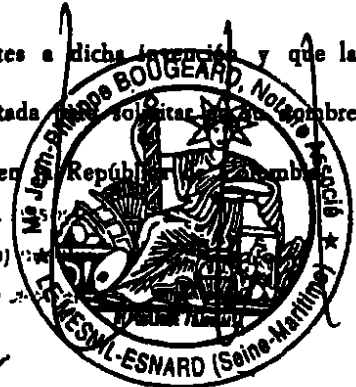
Dominique LEFAY

all rights inherent to said invention, and that the above
mentioned corporation hereby is enabled to apply, in its
name, for the corresponding patent in the Republic of
Colombia.

todos los derechos inherentes a dicha invención y que la
citada sociedad queda facultada para solicitar y obtener
la patente correspondiente en la República de Colombia

Frédéric Champavère, Managing Director

CHAMPAVÈRE.



117

CERTIFICADO NOTARIAL

(INDIVIDUO)

NOTARIAL CERTIFICATE

(INDIVIDUAL)

A los _____ días del mes de _____
de 19____, comparecí _____ personalmente ante mí,
Notario Público,

On this _____ day of _____
19____ personally appeared before me, a Notary Public,

a quien _____ doy fé de conocer y me consta que
la persona descrita y firmante
del documento que precede, declarando ante mí que otor-
ga el mismo para los fines y propósitos que en él se
expresan.

to me known and known to me to be the person
described in and who executed the foregoing document,
and _____ duly acknowledged to me that
executed the same for the uses and purposes
therein expressed.

NOTARY PUBLIC (Notario Público)

Me Jean-Marie VAUCHELLE, Notaire associé
au MESNIL-ESNARD (Seine-Maritime) certifie
sincère et véritable la signature apposée et
contre, comme émanant de _____
CHAMPAGNE



CERTIFICADO NOTARIAL

(INDIVIDUO)

NOTARIAL CERTIFICATE

(INDIVIDUAL)

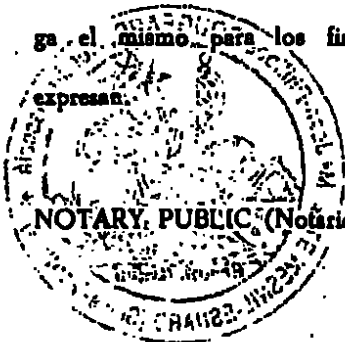
A los _____ días del mes de _____
de 19____, comparecí _____ personalmente ante mí,
Notario Público,

On this 10th day of July
1920 personally appeared before me, a Notary Public,

Traducción Oficial No. 140/00
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCE - ESPAGNOL
Res. Minuterie No. 2680/91

a quien _____ doy fé de conocer y me consta que
la persona descrita y firmante
del documento que precede, declarando ante mí que otor-
ga el mismo para los fines y propósitos que en él se
expresan.

to me known, and known to me to be the person
described in and who executed the foregoing document,
and _____ duly acknowledged to me that
executed the same for the uses and purposes
therein expressed.





CONSULADO GENERAL DE COLOMBIA
PARIS, FRANCIA

No. 3237

Paris, Agosto 16 de 2000

El suscrito **Cónsul General de Colombia en París**, vistos los documentos presentados por los interesados,

CERTIFICA:

Que la señora **Dominique LEFAY**, quien constató que la autenticación de la firma del signatario del documento precedente fue efectuada de conformidad con la ley francesa, ejercía en la fecha las funciones de **Secretaria Administrativa de la Dirección de los Franceses en el Exterior y de los Extranjeros en Francia del Ministerio de Asuntos Exteriores de Francia**, y que su firma corresponde con la registrada en este Consulado;

Que la compañía **JANSSEN CILAG S.A.** es una sociedad constituida de acuerdo con las leyes de la República Francesa y que cumple con su objeto conforme a las mismas;

Que el **Frédéric CHAMPAVERE** quien en su carácter de **Presidente** de la citada compañía suscribe el documento precedente, es su representante legal en este país.

El Cónsul General no asume responsabilidad alguna por el contenido del documento.


Alejandro Borda Rojas
Cónsul General

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

400 30 18:22

LEGATIZACIONES
CAFÉ DE HOGAR D.F.

Pagado Impuesto de Timbre por valor de US\$7,00 (SIETE DOLARES DE LOS ESTADOS UNIDOS DE AMERICA)

Pagados Derechos Consulares por valor de US\$15 (QUINCE DOLARES DE LOS ESTADOS UNIDOS DE AMERICA)

Total: US\$22 (VEINTIDOS DOLARES DE LOS ESTADOS UNIDOS DE AMERICA).

MINISTERIO DE ASUNTOS
EXTERIORES

425817

LEGATIZACIONES
CAFÉ DE HOGAR D.F.

Janssen
JAE 31/31:
324

TRADUCCION OFICIAL No. 141/00 DE UN DOCUMENTO ESCRITO EN
FRANCES, EL CUAL PARA SU IDENTIFICACION SE SELLA CON EL SELLO DEL
TRADUCTOR. ESTA ES UNA TRADUCCION OFICIAL EFECTUADA EL DIA 01 DE
SEPTIEMBRE DEL AÑO 2000 POR JEAN-JACQUES TURPIN, C.E.: 193849 DE
BOGOTA, TRADUCTOR OFICIAL SEGUN RESOLUCION No. 2680/91 DEL 19 DE
DICIEMBRE DE 1991, EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE
COLOMBIA.

Autenticaciones que se hallan a continuación de un documento de traspaso
conferido en inglés y en español por Eddy Jean Edgard Freyne, Frederic Dirk
Deroose y Erwin Coesemans, domiciliados en Janssen Pharmaceutica N.V.
Turnhoutseweg 30, B-2340 Beerse, Bélgica, quienes declaran ser los únicos y
verdaderos inventores de "inhibidores il-5 no-esteroidales, procedimientos para su
preparación y composiciones farmacéuticas que los contienen". Declaran asimismo
ceder y transferir sin reserva ni limitación a la sociedad Janssen Pharmaceutica N.V.,
sociedad organizada y existente de acuerdo con las leyes de Bélgica, domiciliada en
Turnhoutseweg 30, B-2340 Beerse, Bélgica, todos los derechos inherentes a dicha
invención, y que la sociedad queda facultada para solicitar en su nombre la patente
correspondiente en la República de Colombia. Firma ilegible de Eddy Jean Edgard
Freyne, Frederic Dirk Deroose y Erwin Coesemans.

Certificación notarial de presentación personal y legalización de firma de Eddy Jean
Edgard Freyne, Frederic Dirk Deroose y Erwin Coesemans con fecha del 1 de
Agosto del año 2000.

Apostilla (Convención de La Haya del 5 de Octubre de 1961):

1. País: Bélgica

El presente acta

Traducción Oficial No. 141/00
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCOIS - ESPANOL
Res. Minjusticia No. 2680/91

375
312

2. Ha sido firmado por Coppens
3. Obrando en calidad de Notario
4. Con sello /estampilla de (ilegible)

Certificado

5. En Bruselas
6. El 3 de Agosto del 2000
7. Por el Ministerio de Relaciones Exteriores, del Comercio Exterior y de la Cooperación para el Desarrollo.
8. Bajo el número: (28418)
9. Sello / estampilla
10. Firma ilegible

Sello: Ministerio de Relaciones Exteriores, del Comercio Exterior y de la Cooperación para el Desarrollo.

Legalización No. 611 del 10 de Agosto del año 2000 de la firma de C.Mélard, Delegado del Ministerio de Relaciones Exteriores de Bélgica. Pagado el impuesto de timbre. Sello del Consulado de Colombia en Bruselas. Firma y sello de Mauricio González López.

Legalización de la firma de Mauricio González López por el Ministerio de Relaciones Exteriores en Bogotá No. 425810 del 30 de Agosto del año 2000. Firma y sello del Jefe de legalizaciones.

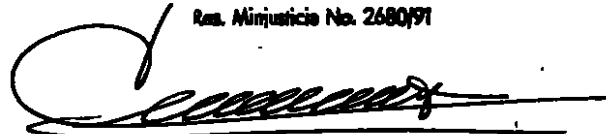
Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para confrontación y a la cual me remito.

Traducción oficial No. 141/00.

Traductor: Jean-Jacques Turpin.

Santafé de Bogotá, D.C., 01 de Septiembre del año 2000.

Traducción Oficial No. 141/00
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCOIS - ESPAGNOL
Reg. Minjusticia No. 2680/91



MINISTERIO DE LA JUSTICIA
EXTERIORES

525967

COMUNICACION A LA AGENCIA EN EL
PUNTO DESEMPEÑO
DE LAS FUNCIONES INDICADAS

PESTON: 2/11/02
2/11/02
-4- P 1 02

JEFE DE LEGALIZACIONES
SANTO DOMINGO D.C.

[Handwritten signature]

Janssen 326
00.058.843
313312

The undersigned,

abajo firmado

Eddy Jean Edgard Freyne
Frederik Dirk Deroose
Erwin Coesemans

Eddy Jean Edgard Freyne
Frederik Dirk Deroose
Erwin Coesemans

CONSULADO DE COLOMBIA
BRUSELAS, BELGICA
NC. 611

10 AOUT 2000

Prevía la confrontación correspondiente DA PE que la firma que aparece en este documento es similar a la registrada en el Ministerio de Relaciones Exteriores de Bélgica. El Consulado no asume responsabilidad por el contenido del documento.

domiciled in

c/o Janssen Pharmaceutica N.V.
Turnhoutseweg 30
B-2340 Beerse, Belgium

c/o Janssen Pharmaceutica N.V.
Turnhoutseweg 30
B-2340 Beerse, Belgica



PAGADO IMPUESTO DE TIMBRE

RUBEN GONZALEZ LOPEZ
Cónsul General de Colombia

hereby state under oath to be the sole and true inventor of

declaramos de ser el inventor de

NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION

AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

INHIBIDORES I L-5 NO ESTEROIDALES, PROCEDIMIENTOS E INTERMEDIARIOS PARA SU PREPARACION Y COMPOSICIONES FARMACEUTICAS QUE COMPREDEN DICHOS INHIBIDORES

state as well

assign, without reservations

Declaramos

asimismo que cedemos

y

or limitation, in favor of

transferimos

sin reserva ni limitación, a favor de la

Janssen Pharmaceutica N.V.

sociedad Janssen Pharmaceutica N.V.

a corporation organized and existing under the laws of Belgium

organizada y existente de conformidad con las leyes de Belgica

domiciled in Turnhoutseweg 30
B-2340 Beerse, Belgium

domiciliada en Turnhoutseweg 30
B-2340 Beerse, Belgica

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Eddy Jean Edgard Freyne

Frederik Dirk Deroose

Erwin Coesemans

MINISTERIO DE RELACIONES EXTERIORES
25810
Janssen

NO SE ASUME RESPONSABILIDAD DEL TEXTO
2000 AGO 30
JEFE DE LEGALIZACION
SANTIA DE BURGUA D.

122
327

314

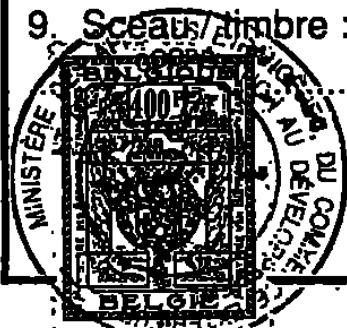
APOSTILLE.

(Convention de La Haye du 5 octobre 1961).

1. Pays : Belgique
Le présent acte public
2. a été signé par COPPENJ.....
3. agissant en qualité de NOTAIRE.....
4. est revêtu du sceau / timbre de VOSSELAAR.....

Attesté

5. à Bruxelles
6. le 03-08-2000.....
7. par le Ministère des Affaires Etrangères, du Commerce
Extérieur et de la Coopération au Développement
8. sous n° 28418.....
9. Sceaux/timbre :
10. Signature :



[Handwritten signature]

12

CERTIFICADO NOTARIAL (INDIVIDUO) NOTARIAL CERTIFICATE (INDIVIDUAL)

A los días del mes de On this 1st day of August 2000
de 19 , comparecí personalmente ante mí 19 personally appeared before me a Notary Public
Notario Público

141/00

Traducción Oficial No. JEAN JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCOES ESPAROL
Reg. Matrícula No. 2680/91

a quien doy fé de conocer y me consta que to me known and known to me to be the person
la persona descrita y firmante described in and who executed the foregoing document
del documento que precede declarando ante mí que otor and duly acknowledged to me that
ga el mismo para los fines y propósitos que en él se executed the same for the uses and purposes
expresan therein expressed

NOTARY PUBLIC (Notario Público)



CERTIFICADO NOTARIAL (INDIVIDUO) NOTARIAL CERTIFICATE (INDIVIDUAL)

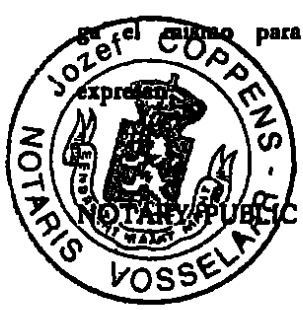
A los días del mes de On this day of
de 19 , comparecí personalmente ante mí 19 personally appeared before me a Notary Public
Notario Público,

Gezien voor echtverklaring van de op
dit stuk geplaatste handtekening van
M
03-08-2000



Brussel, de
Voor de Minister van Buitenlandse Zaken
De Afgevaardigde Ambassadeur
C. MELARD

a quien doy fé de conocer y me consta que to me known, and known to me to be the person
la persona descrita y firmante described in and who executed the foregoing document
del documento que precede declarando ante mí que otor and duly acknowledged to me that
ga el mismo para los fines y propósitos que en él se executed the same for the uses and purposes
expresan therein expressed



NOTARY PUBLIC (Notario Público)



315 328

Industria y Comercio
SUPERINTENDENCIA

INFORME DE PROTOCOLO

Expediente 00-58843

Fecha 8 de Agosto del 2000

Se certifica que

Desde fecha 3 de Diciembre de 1998,
del folio 101.844 al folio 101.889
del libro de Protocolo N° 354, obra el
poder N° 18.901 conferido por JANSSEN
PHARMACEUTICA N.V.

domiciliado(a) en Beerse, Belgica

al doctor JOSE LLORED CAMACHO Y/O JOSE
ANTONIO LLORED Y/O AURA DUEÑAS RODRIGUEZ Y/O
GUSTAVO TAMAYO Y/O ANGELA MARIA RESTREPO
Representante en Santafé de Bogotá D C Los
mismos

Facultad para desistir y sustituir si

Revisado 202022

Carrera 13 No 27-00 Pisos 5 7 y 10
Conmutador 382 0840
Fax 382 2695
E-mail info@sic.gov.co
Bogotá D C Colombia

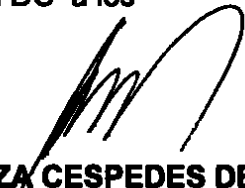
2020
Bogotá DC

Doctor
JOSE ANTONIO LLOREDA
Representante

REFERENCIA	Radicación No	00-58843
	Tramite	002
	Evento	001
	Actuación	416
	Oficio No	0482
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina y en las demás disposiciones vigentes sobre la materia se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial conforme lo establece el artículo 40 de la misma Decisión

Cumplase
Dado en Bogotá DC a los **24 FEB. 2001**


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Bogotá, DC **06-09-2005** El extracto de esta solicitud fue publicado en el número **505**
de la Gaceta de Propiedad Industrial de fecha **27-06-2001** El término hábil señalado por la
ley expiró el **25-09-2001** y SI ☐ NO ☒ se presentaron observaciones por parte de terceros

Carrera 13 No 27-00 Pisos 5 7 y 10
Conmutador 382 0840
Fax 382 2695
E-mail info@sic.gov.co
Bogotá D C Colombia