Industria y Comercio
SUPERINTENDENCIA

SOLICITUD DE PATENTE DE INVENCION

SUPERINDUSTRIA Y COMERCIO
Radicacion : 01000514 00000000 Folios: 329
Fecha (D:M:A) 2001-01-04 15:03:25
Tramite : 002 PATENTES D : REGISTRO/ 411 PRIMER
Dependencia: 2020 DIVISION DE NUEVOS CREACIONES

01 514

DATOS DEL SOLICITANTE

(71) Nombres y Apellidos o Razón Social: WARNER LAMBERT COMPANY

No. de Identificación:

Representante Legal (Persona Jurídica):

País de Domicilio: ESTADOS UNIDOS

Departamento o Estado: NEW JERSEY

Dirección: 201 Tabor Road

Ciudad: MORRIS PLAINS Teléfono:

(74) DATOS DEL APODERADO

Nombre: RODOLFO RODRIGUEZ MADRID

Dirección y Domicilio: Transv 6 No. 27-10 Pent House

Ciudad: BOGOTA D C Teléfono: 341 7003

DATOS DEL INVENTOR

(72) Nombre del Inventor (es): CATHERINE BURNOUF, AMAYA BERECIBAR, MICHEL NAVET.

Identificación: FRANCIA. FRANCIA. FRANCIA.

Dirección: 13, rue de l'Ermitage; 10/10 bis, rue de Fontenay.
1,rue Hector Berlioz

Ciudad: 91390 Morsang-sur-orge, 92340 Bourg-la-Reine, Teléfono:
91460 Marcoussis.

DATOS DE LA PATENTE DE INVENCION

(54) Título de la Invención: PIRAZOLO(4,3-e)DIAZEPINAS SUSTITUIDAS NOVEDOSAS, COMPOSICIONES FARMACEUTICAS QUE LAS CONTIENEN, SU USO COMO PRODUCTOS MEDICINALES Y PROCESOS PARA PREPARARLAS.

PRIORIDAD REIVINDICADA SI [X] NO [ ] TIPO DE PRIORIDAD ANDINA [X] UNIONISTA [ ]

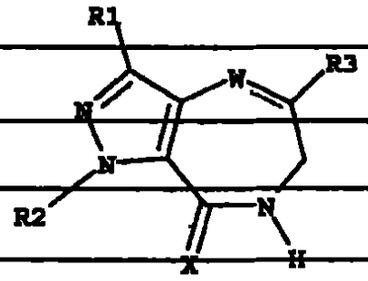
(33) País FRANCIA (32) Fecha 2000/01/05 (31) No. Solicitud 0000095

Para Publicar a los [ ] 6 meses [X] 12 meses [ ] 18 meses a partir de la fecha de la presente solicitud

(51) CLASIFICACION INTERNACIONAL A 61 K 31/551

RESUMEN CON EL OBJETO Y LA FINALIDAD DE LA PATENTE DE MODELO DE UTILIDAD

La invención se relaciona con pirazolo (4,3-e)-diazepinas sustituidas novedosas de la formula general



I

con composiciones farmacéuticas que las contiene, con su uso como productos medicinales y con procesos para prepararlas

ANEXOS DE LA SOLICITUD

Certificado de Existencia y Representación Legal cuando el solicitante sea Persona Jurídica	X
Los poderes debidamente otorgados, o mención de su protocolización ante la SIC (Protocolo No 17877 de Octubre 22/97)	X
Recibo de la tasa respectiva	X
Recibo de la tasa por concepto de excedente de palabras en la publicación	
Si se reivindica prioridad Andina	
Copia de la primera solicitud	
Traducción oficial	
Si se reivindica prioridad Unionista	
Copia certificada primera solicitud	
Nota. Debe presentarse dentro de los tres (3) meses, contados a partir de la fecha de radicación de la solicitud posterior	
Traducción simple	X
Capítulo descriptivo	X
Dibujos, planos necesarios	X
Capítulo reivindicatorio	X
Tarjeta archivo propietarios según formato	X
Tarjeta archivo temático según formato	X
Extracto para publicación según formato	X
Arte final 12 x 12 cms y 6x6 cms	X
Otros Documentos	

SOLICITO LA CONCESION DE LA PATENTE DE MODELO DE UTILIDAD Y DECLARO QUE LA INVENCION ES NUEVA Y DE MI PROPIEDAD

FIRMA

NOMBRE RODOLFO RODRIGUEZ MADRID **CC** 3'792.584-Cartagena **T.P No.** 59363

Folios 2, 3 y 4 de extracto para publicacion

LEGALIZACION
000240
MAQUINA 37
COLEGIO DE ESCRIBANOS
14/10/97
07581

COLEGIO DE ESCRIBANOS CAPITAL FEDERAL REPUBLICA ARGENTINA
ACTA NOTARIAL
ALEJANDRO PORACE
ESCRIBANO

TESTIMONIO

B 008877044

FOLIO 1618.- PRIMER TESTIMONIO.------ ----------

ESCRITURA NUMERO SEISCIENTOS VEINTITRES. En la Ciudad de Buenos Aires, Capital de la República Argentina, a diez de octubre de mil novecientos noventa y siete, ante mi, Escribano Autorizante, titular del Registro Notarial número 1331, COMPARECE el Doctor Daniel SOYTIA argentino, casado, mayor de edad, L E número 4 526 965, domiciliado en Avenida Leandro N Alem 651, 5o piso, de esta Ciudad, persona hábil y de mi conocimiento, doy fe, así como que DICE I - Que por escritura del 14 de octubre de 1996, pasada al folio 1742 del Protocolo del Registro 1586 de esta Ciudad, a cargo del Escribano A Chacra Larrory, la que en su original tengo a la vista y en fotocopia debidamente autenticada, obra agregada al folio 1510 del Protocolo corriente de este Registro, se protocolizó un Poder otorgado por 'WARNER-LAMBERT COMPANY , con domicilio en 201 Tabor Road, Morris Plains, New Jersey 07950, U S A ; a su favor - II - Que viene por la presente a SUSTITUIR el citado mandato, reservándose para si las facultades, a favor de RODRIGUEZ Y ASOCIADOS" y/o Rodolfo RODRIGUEZ MADRID y/o Carlos Julio BUITRAGO BARZON y/o Marina RODRIGUEZ MADRID, con domicilio en Carrera 7a , No 17-64, Of 903, Santa Fe de Bogota, D C , Colombia, para actuar en dicho pais, con las siguientes facultades poder amplio y suficiente para recabar de las autoridades nacionales que corres-

ponda, sean éstas administrativas y/o judiciales, la ob-
tención de Patentes, Marcas, Modelos, Diseños y sus reno
vaciones y realizar todos los trámites conducentes para
proteger los derechos de la mandante, a cuyo efecto los
faculta para efectuar ante dichas autoridades nacionales
administrativas y/o judiciales, todos los trámites necesa-
rios a los objetos indicados; presentar solicitudes ale-
gatos oposiciones, protestas, apelaciones y demandas, de-
sistir, arreglar y transigir; aceptar cesiones y transfe-
rencias; solicitar testimonios, recibir documentos y otros
valores, justificar explotaciones, cobrar y percibir fir-
mar instrumentos públicos, privados y escrituras públicas,
para renunciar o no a las gestiones judiciales, y hacer
cuanto fuere necesario ante las autoridades nacionales,
judiciales y/o administrativas, sea como demandante o como
demandado, para proteger los intereses del mandante, con
facultad de substituir este instrumento y revocar tal
substitución - Se deja constancia que las facultades enu
meradas en este mandato, son meramente ejemplificativas y
no limitativas de otras facultades implícitas, por cuyo
motivo, los mandatarios quedan autorizados para ejercer
sin restricción alguna todos los derechos que acuerde la
le, que se relacionen y/o emerjan y/o que sean consecuen-
cia del objeto del presente poder y ya sea ello en razón
de la legislación que en el futuro se promulgue ' LO

COLEGIO DE ESCRIBANOS — ACTA NOTARIAL

TESTIMONIO

B 008877045

TRANSCRIPTO ES COPIA FIEL, doy fe, de las partes pertinente del mandato relacionado - LEIDA y ratificada, así lo expresó, otorgó, aceptó y firmó el compareciente por ante mi, en prueba de conformidad, de lo que doy fe - SIGUE UNA FIRMA - Está mi sello - Ante mí ALEJANDRO M LIPORACE - CONCUERDA con su matriz que pasó ante mí, ALEJANDRO MARIA LIPORACE, titular del Registro 1331 de esta Ciudad, al folio 1618 del Protocolo del año en curso de este Registro a mi cargo y al que me remito, doy fe - PARA **LOS APODERADOS** expido este **PRIMER TESTIMONIO** en dos fojas de Actuación Notarial números B 008877044 y B 008877045, las que sello y firmo en el lugar y fecha de su otorgamiento, CONSTE -

ALEJANDRO M L PORACE
Matrícu 77





B 008877

26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

4

19971014053

EL COLEGIO DE ESCRIBANOS de la Capital Federal República Argentina en virtud de las facultades que le confieren las Leyes vigentes LEGALIZA la firma y el sello del escribano don ALEJANDRO MARIA LIPORACE obrantes en el documento anexo presentado en el día de la fecha bajo el Nº 002799628 Serie L. La presente legalización no juzga sobre el contenido y forma del documento

Buenos Aires Martes 14 de octubre de 1997

ELENA [illegible] ALENTINIS DE FAILLA
COLEGIO DE ESCRIBANOS
EX CONSEJERA LEGALIZADORA

25 te para recabar de las autoridades nacionales que corres-

MINISTERIO DE RELACIONES EXTERIORES

275150

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

97 OCT 21 PM 12:33

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

ESTE DOCUMENTO CARECE DE VALOR SIN EL TICKET DE MAQUINA ADHERIDO

MINIST DE RR EE
COM INT Y CULTO
LEGALIZACIONES

14/10/97 M000000

CER VARIOS 34 00
CAJA

M01 [illegible]

2435

El suscrito [illegible] certifica que la firma que aparece en el presente documento es auténtica y concuerda con la que obra en nuestros archivos.

ELBA A. STAFFIERI

quién ejerce en la fecha allí expresada las funciones de Departamento de Legalizaciones Ministerio de Relaciones Exteriores

El Cónsul no asume responsabilidad alguna por el contenido de [illegible]

15 OCT 1997

HABILITADO

El Departamento de Legalizaciones de la Cancillería Argentina certifica que la firma que aparece en este documento y fecha [illegible] guarda similitud con la que obra en nuestro registro.

Prof. ELBA A. STAFFIERI
DEPARTAMENTO LEGALIZACIONES

Miguel Muñoz Paladines
Primer Secretario
Encargado Funciones Consulares

IMPORTE: U$n 21.—

Industria y Comercio

SUPERINTENDENCIA

"IT 30 "6^^9 2

SUPERINDUSTRIA Y COMERCIO
Radicacion 01006514 00000000 Folios 509
Fecha (RAD): 2001-01-04 15:03:25
Tramite 002 PATENTES D 1 REGISTRO/ 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

*** O"S I C"A C I O N *****

...ICITANT...	T"O "...^	BANCO	"UCURSAL	CUE"TA	"... P...O	"...^
S...A JE...E I CARDE...^	COMS CH... DE	BA"CO POPULAR	...CO"...	C^ 10 C	31.0 2	650 ^00 ^0

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

CANT	RENTIST CO	CONCEPTO	TOTAL CO"...EPTO
	0005 0 01 SOL' ITUDES	1 TRA"ITES DE SOL DE P..TENTE DE IN T"TAL	$^..., ^ ^. .., ...

SON SC SC ENTOS OCHO MIL PESOS

...O... ...E _____

"C O PC CA"A APL'CADO AL EXPED ENTE ^o _____

Carrera 13 No 27-00 Pisos 5 7 y 10
Conmutador 382 0840
Fax 350 5220
e-mail info@sic.gov.co
www.sic.gov.co
Bogotá D C Colombia

9
6

PIRAZOLO[4,3-e]DIAZEPINAS SUSTITUIDAS NOVEDOSAS, COMPOSICIONES FARMACEUTICAS QUE LAS CONTIENEN, SU USO COMO PRODUCTOS MEDICINALES Y PROCESOS PARA PREPARARLAS

La invención se relaciona con pirazolo[4,3-e]diazepinas sustituidas novedosas, con composiciones farmacéuticas que las contienen, con su uso como productos medicinales y con procesos para prepararlas

Antecedente tecnológico de la invención

El 3',5'-monofosfato de adenosina cíclica (cAMP) es un segundo mensajero intracelular ubicuo, que es intermedio entre un primer mensajero (hormona, neurotransmisor o autocoide) y las respuestas funcionales celulares el primer mensajero estimula la enzima responsable de la síntesis del cAMP, según qué células estén involucradas, el cAMP interviene en numerosas funciones metabólica, contráctil o secretora

Los efectos del cAMP terminan cuando éste es degradado por las fosfodiesterasas de nucleótidos cíclicos, que son enzimas intracelulares que catalizan su hidrólisis en 5'-monofosfato de adenosina inactiva

Se han distinguido al menos 11 familias principales de fosfodiesterasas de nucleótidos cíclicos (PDE) en los mamíferos, numeradas de 1 a 11 de acuerdo con su estructura, su comportamiento cinético, su especificidad para el sustrato o su sensibilidad a los efectores (Beavo J A et al (1990) Trends Pharmacol Sci 11, 150-155 Beavo J A et al (1994) Molecular Pharmacol 46, 399-405) Las enzimas PDE4 son específicas para el cAMP

Son conocidos los compuestos inhibidores de fosfodiesterasa no específica, que inhiben varias familias de enzimas Éste es el caso de ciertas metil xantinas tales como la teofilina Estos compuestos tienen un bajo índice terapéutico, en particular debido a su acción sobre tipos de PDE presentes en células que no son las células objetivo A la inversa, ciertas familias de PDE pueden ser inhibidas selectivamente por diversos agentes farmacológicos la hidrólisis de nucleótidos cíclicos se hace más lenta y su concentración aumenta entonces solamente en las células en las cuales se halla el tipo de PDE que es sensible al inhibidor

Se muestra una ventaja específica para las fosfodiesterasas 4 (PDE4), que han sido identificadas en muchos tejidos que incluyen el sistema nervioso central, el corazón, el endotelio

vascular, el músculo liso vascular y el de las vías respiratorias, las líneas mieloides y las líneas linfoides

Un aumento en el cAMP en las células involucrado en la inflamación inhibe su activación inhibición de la síntesis y liberación de los mediadores en los mastocitos, los monocitos, los eosinófilos y los basófilos polimorfonucleares, inhibición de la quimiotaxis y la desgranulación de los neutrófilos y los eosinófilos polimorfonucleares, inhibición de la proliferación y la diferenciación de los linfocitos

Las citoquinas, en particular las TNF y las interleucinas, producidas por diversos tipos de leucocitos tales como los linfocitos T, los monocitos y los eosinófilos polimorfonucleares, tienen un importante papel en el inicio de manifestaciones inflamatorias, en particular en la respuesta a la estimulación por un alergeno en las vías respiratorias

Más aún, el cAMP reduce la tonicidad de las fibras del músculo liso en las vías respiratorias

Se podría esperar entonces que los inhibidores de PDE4 selectivos tengan actividad terapéutica como productos medicinales antiinflamatorios y antialérgicos, y en el

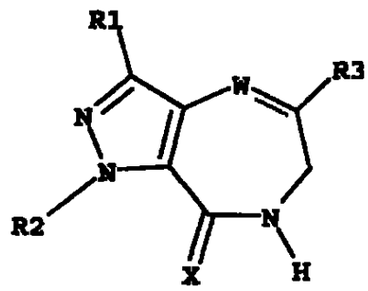
tratamiento de diversas enfermedades respiratorias tales como asma, enfisema y bronquitis crónica

Se ha realizado una amplia investigación durante varios años de la producción y el desarrollo de potentes inhibidores de PDE4 Esto se considera difícil debido al hecho de que muchos inhibidores potenciales de PDE4 no están desprovistos de actividad sobre las fosfodiesterasas de otras familias

En la actualidad, la falta de selectividad de los inhibidores de PDE4 representa entonces un importante problema, dado el nivel de las funciones reguladas por el cAMP Por lo tanto existe una necesidad de inhibidores de PDE4 potentes y selectivos, es decir inhibidores que no tengan ninguna acción con respecto a PDE que pertenezcan a otras familias y particularmente a PDE que regulen el cGMP

Resumen de la Invención

La invención se relaciona con pirazolo[4,3-e]diazepinas sustituidas con la fórmula general I siguiente



I

en donde

R_1 se elige de los siguientes grupos

hidrógeno,

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

cicloalquilo que contiene de 3 a 6 átomos de carbono,

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nC(S)R_B$, $(CH_2)_nC(S)OR_B$, $(CH_2)_nC(S)SR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, $(CH_2)_nNR_DC(O)NR_DR_B$ o $(CH_2)_nZ$, en donde

R_A se elige de alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono

cicloalquilo que contiene de 3 a 6 átomos de carbono,

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

15

12

R_B y R_C, que pueden ser idénticos o diferentes, se eligen de hidrógeno,

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

cicloalquilo que contiene de 3 a 6 átomos de carbono,

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono, siendo posible que R_B y R_C formen un anillo que contiene de 5 a 7 átomos de carbono que pueden incluir uno o más heteroátomos elegidos de S, N y O,

R_D es hidrógeno o alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

Z es un halógeno, y

n es un número entero de 0 a 4 inclusive,

R_2 se elige de los siguientes grupos

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

cicloalquilo que contiene de 3 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_mOR_B$, $(CH_2)_mCF_3$, $(CH_2)_mC(O)R_B$, $(CH_2)_mCOOR_B$, $(CH_2)_mOC(O)R_A$, $(CH_2)_mSR_B$, $(CH_2)_mC(S)R_B$, $(CH_2)_mC(S)OR_B$, $(CH_2)_mC(S)SR_B$, $(CH_2)_mNR_BR_C$,

14

$(CH_2)_mC(O)NR_BR_C$, $(CH_2)_mNR_CC(O)R_B$, $(CH_2)_mNR_DC(O)NR_DR_B$ o $(CH_2)_mZ$, en donde

R_A, R_B, R_C, R_D y Z son lo definido anteriormente,

y m es un número entero de 1 a 4 inclusive,

n es un número entero de 0 a 4 inclusive,

R_3 se elige de los siguientes grupos

hidrógeno,

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

cicloalquilo que contiene de 3 a 6 átomos de carbono,

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

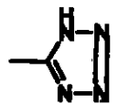
alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nC(S)R_B$, $(CH_2)_nC(S)OR_B$, $(CH_2)_nC(S)SR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, $(CH_2)_nNR_DC(O)NR_DR_B$ o $(CH_2)_nZ$, en donde

R_A, R_B, R_C, R_D y n son lo definido anteriormente,

los grupos arilo, arilalquilo, y alquilarilo definidos anteriormente son no sustituidos o sustituidos en el grupo arilo con 1, 2, o 3 grupos elegidos de

halógeno, hidroxilo, NO, NO_2, CN, alcoxi que contiene de 1 a 4 átomos de carbono, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, $(CH_2)_nHNSO_2R_B$, $(CH_2)_nN(SO_2R_B)_2$, CO_2R_B, CF_3 y



en donde R_B, R_C y n son lo definido anteriormente, y

la línea de puntos presente en la fórmula I indica que la unión entre W y el carbono en la posición 5 puede ser

- una sola unión, en cuyo caso W representa un átomo de nitrógeno sustituido con un átomo de hidrógeno,
- una unión doble, y en este caso W representa un átomo de carbono no sustituido,

X es S, O, N-CN o N-R_8 en donde R_8 es lo definido anteriormente,

así como los óxidos, las formas tautómeras y los isómeros ópticos correspondientes o los derivados farmacéuticamente aceptables de los compuestos de la fórmula I, con la salvedad de que cuando

R_1 representa un grupo metilo, R_2 un grupo etilo, W es N, X es un átomo de oxígeno y la unión entre W y el átomo de carbono en la posición 5 es una unión doble,

entonces

R_3 no es ni un grupo fenilo no sustituido ni un grupo fenilo que lleva un átomo de flúor en una posición orto como único sustituyente

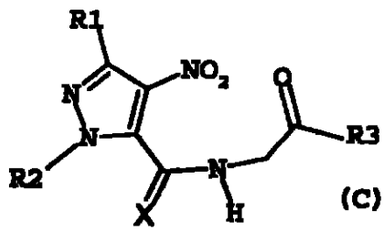
Los compuestos de la invención tienen propiedades inhibidoras de la liberación de PDE4 y/o TNFα Algunos de estos compuestos son también inhibidores selectivos de subtipos de PDE4 Los compuestos de la invención pueden usarse en el tratamiento de enfermedades que incluyen el cáncer, el síndrome de inmunodeficiencia adquirida, la fibrosis, las cicatrices excesivas que incluyen las cicatrices dérmicas excesivas tales como las cicatrices dérmicas normales o anormales posteriores a heridas o cirugías, osteoartritis, osteoporosis, esclerosis múltiple, ans edad, dorsos ón, dermatitis atón ca, artr t s

reumatoidea, ataque séptico, enfermedades inmunes que incluyen lupus eritematoso diseminado, psoriasis, rechazo de injertos y rinitis alérgica, así como enfermedades que involucran la producción de TNFα y más particularmente en el tratamiento de enfermedades inflamatorias tales como asma, bronconeumopatía obstructiva crónica (CODP), lesiones posisquémicas, hipertensión pulmonar, insuficiencia cardíaca congestiva, síndrome de insuficiencia respiratoria aguda, y enfermedades inflamatorias crónicas del intestino (IBD) tales como la enfermedad de Crohn y la colitis ulcerativa

La invención también se relaciona con un proceso para sintetizar un compuesto de la fórmula general I, el mencionado proceso se caracteriza porque comprende

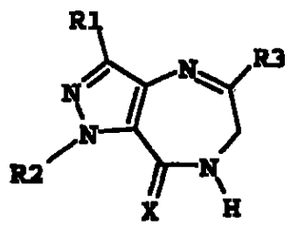
1) cuando, en la fórmula I, X es O o S, W es N y la unión entre W y el átomo de carbono en la posición 5, simbolizada por ═══, es una unión doble

- la ciclización de un compuesto de la fórmula general (C)



(C)

en donde R_1, R_2, R_3 y X tienen el significado dado anteriormente, para dar un intermedio sintético o un compuesto final de la fórmula general D,



(D)

en donde R_1, R_2, R_3 y X tienen los significados dados anteriormente

2) cuando, en la fórmula I, X es S, W es N y la unión entre W y el átomo de carbono en la posición 5, simbolizado por

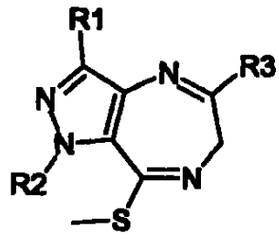
═══, es una union doble

- la tionación de un compuesto de la fórmula general (D), en donde R_1, R_2 y R_3 tienen el significado dado anteriormente y X es O, para dar un compuesto de la fórmula I en donde la unión entre W y el átomo de carbono en la posición 5 es una unión doble, W es N y X es azufre,

3) cuando, en la fórmula I, X es N-CN, W es N y la unión entre W y el átomo de carbono en la posición 5, simbolizado por

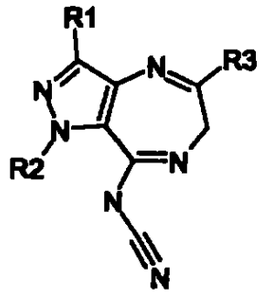
═══, es una unión doble

- la reacción de un compuesto de la fórmula general (G)



(G)

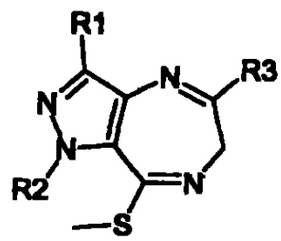
en donde R_1, R_2 y R_3 tienen el significado dado anteriormente, con un compuesto de la fórmula H_2N-CN, para dar un compuesto de la fórmula general F siguiente



(F);

4) cuando, en la fórmula I, X es N-R_8, W es N y la unión entre W y el carbono en la posición 5, simbolizada por ═══, es una unión doble

- la reacción de un compuesto de la fórmula general (G)



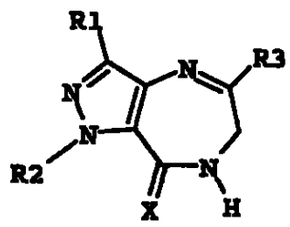
(G)

en donde R_1, R_2 y R_3 son lo definido anteriormente, con un compuesto de la fórmula H_2N-R_8, en donde R_8 es lo definido anteriormente,

para dar un compuesto de la fórmula I en donde la unión entre W y el átomo de carbono en la posición 5 es una unión doble, W es N y X es N-R_8 (J Med Chem , 42, 1999 2909-2919)

5) cuando, en la fórmula I, W es NH y la unión entre W y el átomo de carbono en la posición 5 es una sola unión

- la reacción de un compuesto de la fórmula general (D)



(D)

en donde R_1, R_2, R_3 y X son lo definido anteriormente, con un agente reductor, para dar un compuesto de la fórmula I en donde W es NH y la unión entre W y el átomo de carbono en la posición 5 es una sola unión

La invención también se relaciona con una composición farmacéutica que comprende al menos un compuesto de la fórmula general I definido anteriormente, en combinación con un soporte farmacéuticamente aceptable

La invención también se relaciona con el uso de una pirazolo[4,3-e]diazepina sustituida de la fórmula general I como un producto medicinal

La invención también se relaciona con el uso de una pirazolo[4,3-e]diazepina sustituida de la fórmula general I para preparar un producto medicinal para tratar enfermedades que se relaciona con una terapia con un inhibidor de la fosfodiesterasa 4

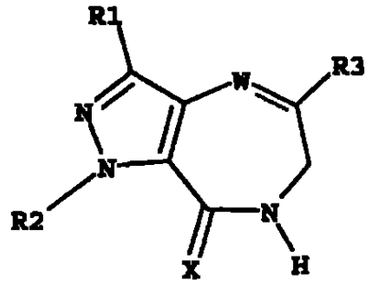
La invención también se relaciona con un método para tratar una enfermedad que se relaciona con una terapia con un inhibidor de la fosfodiesterasa 4, el método mencionado comprende la administración de una concentración efectiva de un compuesto de la fórmula I a un paciente

La invención también se relaciona con el uso de una pirazolo[4,3-e]diazepina sustituida de la fórmula general I para la preparación de un producto medicinal destinado para el tratamiento de mamíferos y particularmente para el tratamiento de humanos, especialmente un producto medicinal destinado para el tratamiento de condiciones que incluyen el cáncer, síndrome de inmunodeficiencia adquirida, fibrosis, cicatrices excesivas que incluyen cicatrices dérmicas excesivas tales como cicatrices dérmicas normales o anormales después de heridas o

cirugías, osteoartritis, osteoporosis, esclerosis múltiple, ansiedad, depresión, dermatitis atópica, artritis reumatoidea, ataque séptico, enfermedades inmunes que incluyen lupus eritematoso diseminado, psoriasis, rechazo de injertos, rinitis alérgica, enfermedades que involucran la producción de TNFα y más particularmente enfermedades inflamatorias tales como asma, bronconeumopatía obstructiva crónica (COPD), lesiones posisquémicas, hipertensión pulmonar, insuficiencia cardíaca congestiva, síndrome de insuficiencia respiratoria aguda, y enfermedades inflamatorias crónicas del intestino (IBD) tales como la enfermedad de Crohn y la colitis ulcerativa

Descripción Detallada de la invención

La presente invención se relaciona entonces con los compuestos de la fórmula general I

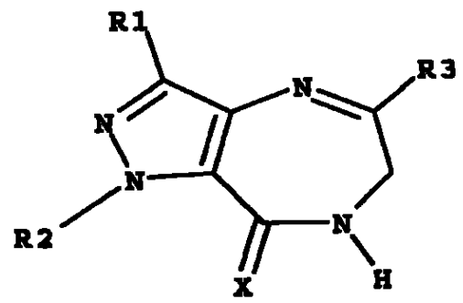


I

en donde la línea de puntos, X, W, R_1, R_2 y R_3 son lo definido anteriormente

Los compuestos de la fórmula I precedente en donde W representa un átomo de nitrógeno no sustituido y la unión entre W y el carbono en la posición 5, simbolizada por ═══, es una unión doble, son preferidos

Entre los compuestos de la fórmula general I que son preferidos, están los compuestos correspondientes a la fórmula general II



II

en donde

R_1 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono

un grupo alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un

grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

un grupo alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, o $(CH_2)_nZ$, en donde

R_A se elige de alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

ciloalquilo que contiene de 3 a 6 átomos de carbono

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,
arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,
alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,
alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono

R_B y R_C, que pueden ser idénticos o diferentes, se eligen de hidrógeno,
alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,
cicloalquilo que contiene de 3 a 6 átomos de carbono,
alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,
arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

R_B y R_C posiblemente forman un anillo que contiene de 5 a 7 átomos que pueden incluir uno o más heteroátomos elegidos de S, N u O,

Z es un halógeno, y

n es un número entero de 0 a 4 inclusive,

R_2 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

$(CH_2)_nCF_3$, en donde n es un número entero de 0 a 4 inclusive,

metilciclopropilo,

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono

o un grupo $(CH_2)_mOR_B$ y $(CH_2)_mCO_2R_B$, en donde m es un número entero de 1 a 3 inclusive y R_B es lo descripto anteriormente,

R_3 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

un grupo alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

un grupo alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

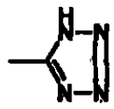
un grupo alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_nOR_B$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$ y $(CH_2)_nNR_CC(O)R_B$, en donde

R_A, R_B, R_C, R_D y n son lo definido anteriormente,

los grupos arilo, arilalquilo, y alquilarilo definidos anteriormente son no sustituidos o sustituidos en el grupo arilo con 1, 2, o 3 grupos elegidos de

halógeno, hidroxilo, NO, NO_2, CN, alcoxi que contiene de 1 a 4 átomos de carbono, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, $(CH_2)_nHNSO_2R_B$, $(CH_2)_nN(SO_2R_B)_2$, CO_2R_B, CF_3 y



en donde R_B, R_C y n son lo definido anteriormente, y X es O, S o NCN

La invención también se relaciona particularmente con los compuestos de la fórmula general II en donde

R_1 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono

un grupo alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono

un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_nOR_B$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, o $(CH_2)_nZ$, en donde

R_A se elige de alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

R_B y R_C, que pueden ser idénticos o diferentes, se eligen de hidrógeno,

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

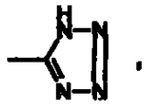
arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,
alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,
n es un número entero de 0 a 4 inclusive,

R_2 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono o un grupo $(CH_2)_mO$ o $(CH_2)_mCO_2H$, en donde m es un número entero de 1 a 3 inclusive,

R_3 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,
un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,
un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,
un grupo arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre
un grupo alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

los grupos arilo, arilalquilo, y alquilarilo definidos anteriormente son no sustituidos o sustituidos en el grupo arilo con 1, 2, o 3 grupos elegidos de

halógeno, hidroxilo, NO, NO_2, CN, alcoxi que contiene de 1 a 4 átomos de carbono, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, CO_2R_B, CF_3 y



en donde R_B, R_C y n son lo definido anteriormente y X es O, S, o NCN

La invención también se relaciona más particularmente con los compuestos de la fórmula general II en donde

R_1 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono,

un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

un grupo alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 3 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

R_2 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono,

R_3 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono,

un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre, preferentemente fenilo o piridilo, los grupos arilo son no sustituidos o sustituidos con 1, 2, o 3 grupos, que pueden ser idénticos o diferentes, elegidos de NH_2, halógeno, metoxi, hidroxilo, CN, CH_3 y CF_3, y

X es O, S o NCN

La invención también preferentemente se relaciona con compuestos de la fórmula general II en donde

R_1 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono,

R_2 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono o un grupo $(CH_2)_nOH$, en donde n es un número entero de 1 a 4 inclusive,

R_3 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono, un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono, un grupo arilo elegido de fenilo y tienilo, que puede ser no sustituido o sustituido con un grupo elegido de halógeno, hidroxilo, metoxi, NH_2 y CH_3 y

X es S u O

La invención también se relaciona preferentemente con los compuestos de la fórmula general I en donde

R_1 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono

R_2 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono o un grupo $(CH_2)_nOH$, en donde n es un número entero de 1 a 4 inclusive,

R_3 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono, un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono, un grupo arilo elegido de fenilo y tienilo, que puede ser no sustituido o sustituido con un grupo elegido de halógeno, hidroxilo, metoxi, NH_2, CH_3, y

X es S

Entre los grupos definidos anteriormente, los siguientes sutituyentes son particularmente preferidos

El grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono y preferentemente de 1 a 4 átomos de carbono. Ejemplos de tales grupos son, entre otros, metilo

etilo, n-propilo, e isopropilo, terc-butilo, n-butilo, sec-butilo e isobutilo

El grupo alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono, preferentemente de 2 a 4 átomos de carbono Ejemplos de ellos comprenden propilideno y butilideno

El grupo alquilcicloalquilo que comprende un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono, particularmente de 1 a 4 átomos de carbono, y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono Ejemplos de ellos incluyen metilciclopropilo, metilciclobutilo y metilciclohexilo

El grupo cicloalquilo que comprende de 3 a 6 átomos de carbono Ejemplos de ellos son ciclopropilo, ciclopentilo y ciclohexilo

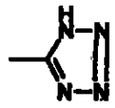
El grupo arilo es un grupo aromático que contiene de 5 a 10 átomos de carbono Ejemplos de tales grupos son fenilo, bencilo, tolilo y naftilo Este grupo arilo puede optativamente ser interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre El término "interrumpido" significa que el heteroátomo puede reemplazar a un átomo de

carbono del anillo Ejemplos de tales grupos que contienen un heteroátomo son, entre otros, tienilo y piridilo

El término alquilarilo corresponde a un grupo que contiene un grupo alquilo y un grupo arilo definidos anteriormente, unidos al resto de la molécula a través del grupo alquilo

El término arilalquilo corresponde a un grupo que contiene un grupo alquilo y un grupo arilo definidos anteriormente, unidos al resto de la molécula a través del grupo arilo

Los grupos arilo, alquilarilo y arilalquilo definidos anteriormente pueden ser no sustituidos o sustituidos en el grupo arilo con 1, 2 o 3 grupos elegidos de,
halógeno, hidroxilo, NO, NO_2, alcoxi que contiene de 1 a 4 átomos de carbono, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, $(CH_2)OR_B$, $(CH_2)_nNHSO_2R_B$, CO_2R_B, CF_3 y



en donde R_B, R_C y n son lo definido anteriormente

Halógeno comprende cloro, bromo, flúor y yodo

Los compuestos de la siguiente lista están entre los compuestos preferidos de la presente invención

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Bromofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1,3-Dimetil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Metoxifenil)-1,3-dimetil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Bromofenil)-1,3-dimetil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-naft-2-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(3-Clorotien-2-il)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

Metil 3-(1-etil-3-metil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)propanoato,

1-Etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Clorofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(4-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-fluorofenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(3-Bromofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Isopropil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)1-Etil-3-metil-5-fenil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-(2-Hidroxietil)-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

1-Etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(3-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(2-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(2-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-fenil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona, isómero 1,

1-Etil-3-metil-5-fenil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona, isómero 2,

3-Metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-metil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(3-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-3-metil-1-propil-6,7-dihidro-1H-pirazolo[4,3-1][1,4]diazepin-8-ona,

3-Metil-5-fenil-1-(2,2,2-trifluoroetil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1,5-Dietil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-Ciclohexil-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)1-Etil-3-metil-5-pirid-4-il-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-metil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Dietilaminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

N-[4-(1-Etil-3-metil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)fenil]acetamida,

4-(1-Etil-3-metil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)-benzonitrilo,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

1-Etil-3-isopropil-5-(4-pirrolidin-1-il-fenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(2,4-Dimetoxifenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3-Isopropil-1-propil-5-(4-pirrolidin-1-il-fenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(2,4-Dimetoxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3,5-Di-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

47

3-terc-Butil-1-etil-5-(4-pirrolidin-1-il-fenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-5-(2,4-dimetoxifenil)-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-terc-Butil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3-terc-Butil-1-propil-5-(4-pirrolidin-1-il-fenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-5-(2,4-dimetoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-metil-5-pirid-3-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-pirid-2-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-ilcianamida

N-[4-(1-Etil-3-metil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)fenil]-(fenilsulfonil)bencensulfonamida,

42

(1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-il)metilamina,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Ciclopentil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Ciclopropilmetil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Ciclobutilmetil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Alil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-metil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

(±)3-sec-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-5-fenil-1-propil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexil-1-etil-5-fenil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-5-fenil-1-propil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][2,4]diazepin-8-ona,

3-Ciclohexilmetil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

Etil éster del ácido 1-etil-8-oxo-5-fenil-1,6,7,8-tretrahidropirazolo[4,3-e][1,4]diazepin-3-carboxílico,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidenciamida,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e]diazepin-8-ona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-Isopropil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

45

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

(±)3-sec-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(±)3-sec-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-(3,4,5-trimetoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(3-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-(2,3,4-trimetoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3,5-difenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(4-Hidroxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(2,6-Dimetoxifenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

46

3-Etoximetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

Entre los compuestos preferidos definidos anteriormente, los siguientes compuestos son preferidos

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
5-(4-Bromofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
1-Etil-3-metil-5-naft-2-il-6,7-dihidro-1H-pirazolo[3,3-e][1,4]diazepin-8-ona,
5-(3-Clorotien-2-il)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
Metil 3-(1-etil-3-metil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)propanoato,
5-(4-Clorofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
5-(4-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
1-Etil-5-(4-fluorofenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
5-(3-Brmofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-(2-Hidroxietil)-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

1-Etil-5-(3-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(2-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(2-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butill-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(3-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-3-metil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Metil-5-fenil-1-(2,2,2-trifluoroetil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-Ciclohexil-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-metil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-metil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

49

5-(2,4-Dimetoxifenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1h-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

5-(2,4-Dimetoxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazapin-8-ona,

3,5-Di-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

3-terc-Butil-5-(2,4-dimetoxifenil)-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-terc-Butil-8-oxo-1-propil-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

3-terc-Butil-5-(2,4-dimetoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-metil-5-pirid-3-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-pirid-2-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-ilcianamida,

N-[4-(1-Etil-3-metil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)fenil]-(fenilsulfonil)bencensulfonamida,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-terc-Butil-1-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

1-Ciclopropilmetil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Alil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

57

3-terc-Butil-1-etil-5-(4-trifluorometilenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

(±)3-sec-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-5-fenil-1-propil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-etil-5-fenil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

55

52

3-Ciclohexil-5-fenil-1-propil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexilmetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

Etil éster del ácido 1-etil-8-oxo-5-fenil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-3-carboxílico,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

1-Etil-3-isopropil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-Isopropil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

(±)3-sec-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(±)3-sec-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-(3,4,5-trimetoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(3-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3,5-difenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Hidroxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
3-Etoximetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

Entre los compuestos preferidos definidos anteriormente, los siguientes compuestos son preferidos

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,
1-Etil-5-(2-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazapin-8-ona,
3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,
1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,
5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,
5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-Ciclohexil-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-metil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-metil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

5-(2,4-Dimetoxifenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

5-(2,4-Dimetoxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3,5-Di-terc-Butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)-benzonitrilo,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-ilcianamida,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(±)3-sec-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-Isopropil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

(±)3-sec-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-(3,4,5-trimetoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(3-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3,5-difenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(4-hidroxifenil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Hidroxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Etoximetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

Entre los compuestos preferidos definidos anteriormente, los siguientes compuestos son preferidos

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

62

59

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

3,5-Di-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

68

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-ilcianamida,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

(±)3-sec-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-5-(4-hidroximetil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Hidroxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

Entre los compuestos preferidos de la presente invención, los compuestos siguientes son particularmente preferidos

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-Isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

Derivados de l s compuestos de la invención

Los compuestos usados en la invención incluyen los solvatos, los hidratos, las sales farmacéuticamente aceptables y los polimorfos (estructuras de cristales diferentes) de los compuestos de acuerdo con la invención, que están designados como los derivados farmacéuticamente aceptables de ellos

Las sales farmacéuticamente aceptables incluyen, por ejemplo acetato, bencensulfonato, benzoato, bicarbonato, bitartrato, bromuro, acetato de calcio, camsilato, carbonato, cloruro, citrato, diclorhidrato, edetato, edisilato, estolato, esilato, fumarato, gluceptato, gluconato, glutamato, glicoloilarsanilato, hexilresorcinato, hidrabamina, bromhidrato, clorhidrato, hidroxinaftoato, yodato, isetionato, lactato, lactobionato, malato, maleato, mandelato, mesilato, metil bromuro, metil nitrato, metil sulfato, mucato, napsilato, nitrato, pamoato (embonato), pantotenato, fosfato/difosfato, poligalacturonato, salicilato, estearato, subacetato, succinato, sulfato, tanato, tartrato, teoclato, trietiodida, benzatina, cloroprocaína, colina, dietanolamina, etilendiamina, meglumina, procaína, aluminio, calcio, litio, magnesio, potasio, sodio y zinc (ver también "Sales Farmacéuticas", por Berge S M et al, (1997) J Pharm Sci 66

1-19, cuyo contenido se incorpora en la presente invención como referencia)

El uso de una prodroga de un compuesto de acuerdo con la invención también está contemplado (Ver en particular Bundgaard, et al, Acta Pharm Suec , 1987, 24 233-246)
Las mezclas de los compuestos también son consideradas

Formulación farmacéutica de los compuestos de la invención

Los compuestos de la invención se administran en la forma de composiciones que son apropiadas para la naturaleza y la gravedad de la enfermedad que se ha de tratar La dosificación diaria en el hombre es generalmente entre 2 mg y 1 g del producto, lo cual puede ser absorbido en una o más ingestiones Las composiciones se preparan mediante métodos que son comunes para los expertos en el arte y generalmente comprenden del 0,5% al 60% en peso del principio activo (compuesto de la fórmula I) y del 40% al 99,5% en peso de un vehículo farmacéuticamente aceptable Las composiciones de la presente invención se preparan entonces en formas que son compatibles con la vía de administración deseada A modo de ejemplo, están contempladas las siguientes formas, aunque la lista que figura a continuación no es taxativa

65

1) Formas para administración oral

Tabletas, cápsulas, sachets de polvo para suspensión bebible, cápsulas de gel, cápsulas de gel gastro-resistentes, formas de liberación sostenida, emulsiones, cápsulas de oblea de HPMR o cápsulas de gel, liofilizatos para ser fundidos debajo de la lengua, soluciones bebibles, suspensiones y sachets de polvo para una solución bebible

Los polvos, tabletas, cápsulas o formas encapsuladas preferentemente contienen del 5% al 70% del principio activo Los soportes adecuados son, por ejemplo, carbonato de magnesio, estearato de magnesio, talco, lactosa, azúcar, pectina, dextrina, almidón, goma tragacanto, metilcelulosa, carboximetilcelulosa de sodio, cera de bajo punto de fusión, manteca de cacao y similares

Las tabletas, polvos, y cápsulas pueden usarse como una dosificación única para administración oral

En los polvos, el soporte es un sólido finamente dividido, que es una mezcla con el compuesto finamente dividido de la fórmula general I

En las tabletas, el compuesto activo se mezcla con el soporte que tiene las propiedades de unión requeridas en la cantidad

adecuada, y con la mezcla luego se fabrican tabletas de la forma y tamaño requeridos

Las soluciones acuosas para la administración oral pueden prepararse disolviendo el principio activo y agregando, si es necesario, colorantes, mejoradores del sabor, saborizantes, estabilizadores, espesantes, etc A modo de ejemplo, el principio activo puede dispersarse en la forma de un polvo finamente dividido en agua con un material viscoso tal como gomas sintéticas, resinas, metilcelulosa, carboximetilcelulosa de sodio y otros agentes de suspensión conocidos en el campo farmacéutico

2) Formas para administración parenteral

Vía Intravenosa

Soluciones acuosas, soluciones en agua/co-solvente, soluciones usando uno o más agentes solubilizantes, suspensiones coloidales, emulsiones, suspensiones nanoparticuladas que pueden usarse para inyectar formas de liberación sostenida, formas dispersadas y liposomas

Las soluciones estériles del principio activo en agua y/o propilenglicol pueden mencionarse como ejemplos de preparaciones líquidas que son adecuadas para la administración parenteral Las preparaciones líquidas pueden

también formularse en la forma de soluciones acuosas de polietilenglicol

Vía Subcutánea/intramuscular

Además de las formas que pueden usarse por vía intravenosa que también pueden usarse para las vías subcutánea e intramuscular, también se pueden usar otros tipos de formas tales como suspensiones, formas dispersadas, geles de libreación sostenida e implantes de liberación sostenida

3) Formas para administración tópica,

Entre las formas tópicas más comunes están las cremas, geles (fases acuosas gelificadas con polimeros), parches, que son vendas para ser adheridas directamente a la piel y que pueden usarse para tratar dermatosis sin penetración percutánea de la sustancia activa, aspersiones, emulsiones y soluciones

4) Formas para administración pulmonar

En esta categoría se distinguen formas tales como soluciones para aspersiones, polvos para inhaladores y otras formas adecuadas

5) Formas para administración nasal

Éstas se relacionan especialmente con soluciones o suspensiones para gotas

6) Formas para administración rectal

Se seleccionan supositorios y geles, entre otros

Para la preparación de supositorios, una cera de bajo punto de fusión, tal como una mezcla de glicéridos de ácidos grasos y manteca de cacao, se funde en una primera etapa, y el principio activo luego se dispersa en ella, por ejemplo con agitación mecánica La mezcla homogénea fundida luego se vierte en moldes de la forma apropiada y luego se la deja enfriar y solidificar

También se contempla usar formas que permiten la administración de soluciones oftalmológicas o que permiten la administración del principio activo a través de la vía vaginal

Otra categoría importante de formas farmacéuticas que se pueden usar en el contexto de la presente invención se relaciona con formas para mejorar la solubilidad del principio activo A modo de ejemplo, se contempla usar soluciones acuosas de ciclodextrina, y más particularmente formas que comprenden hidroxipropil beta ciclodextrina Una revisión detallada de este tipo de forma farmacéutica se da en el artículo publicado con la referencia *Periódico de la Ciencia*

32

69

Farmaçeutica, 1142-1169, 85 (11), 1996, e incorporado en la presente solicitud de patente como referencia

Las diversas formas farmacéuticas recomendadas anteriormente se describen en detalle en el libro "Pharmacie galénique [Pharmaceutical pharmacy]", por A Lehir (publicado por Masson, 1992 (6ª edición)), que se incorpora en la presente solicitud de patente como referencia

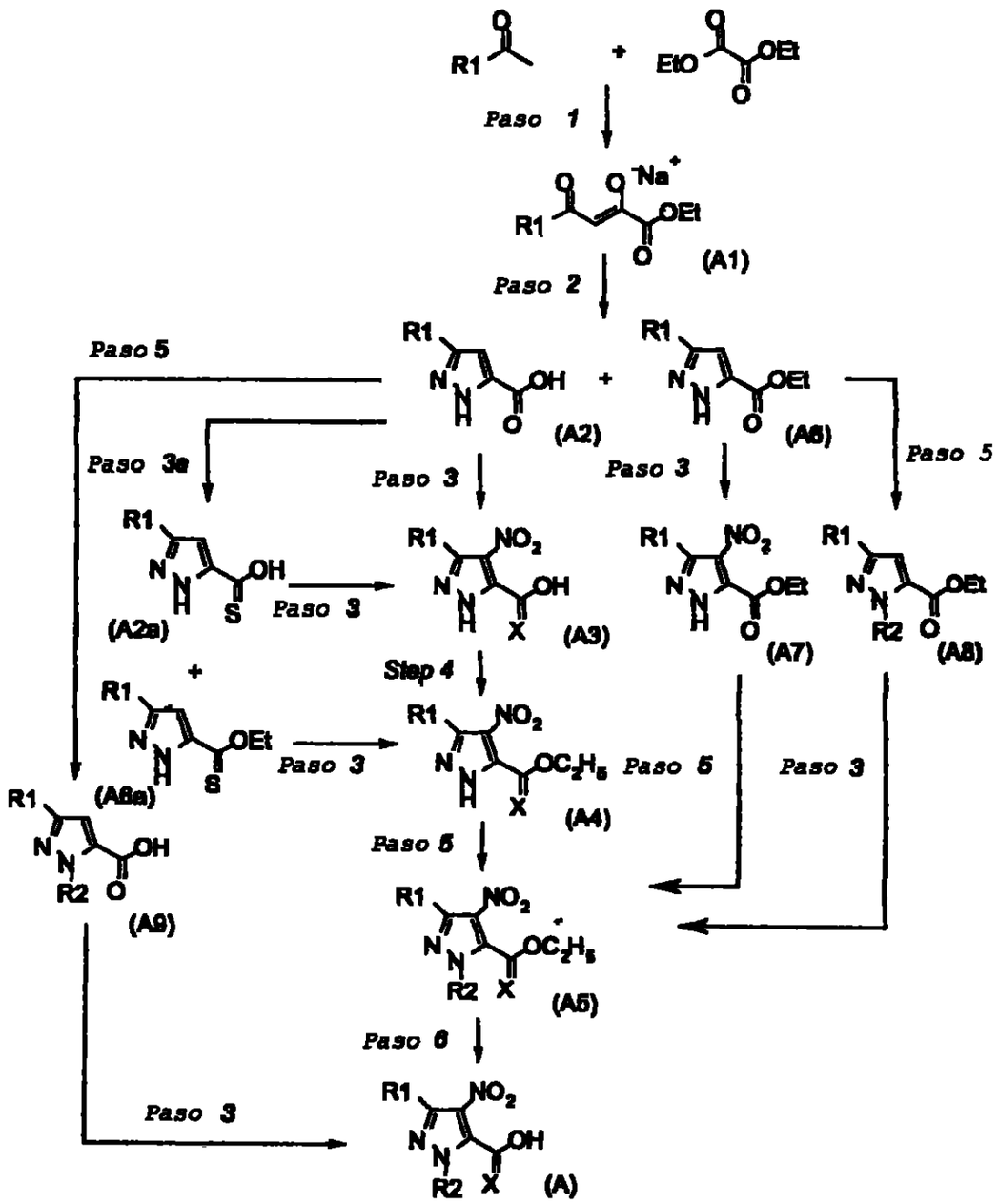
Síntesis de los compuestos de la presente invención

Un objeto de la invención es también un proceso para preparar los compuestos de acuerdo con la invención, que se ilustra en los esquemas de reacción que figuran a continuación Los materiales iniciales están comercialmente disponibles o pueden ser sintetizados mediante métodos estándar

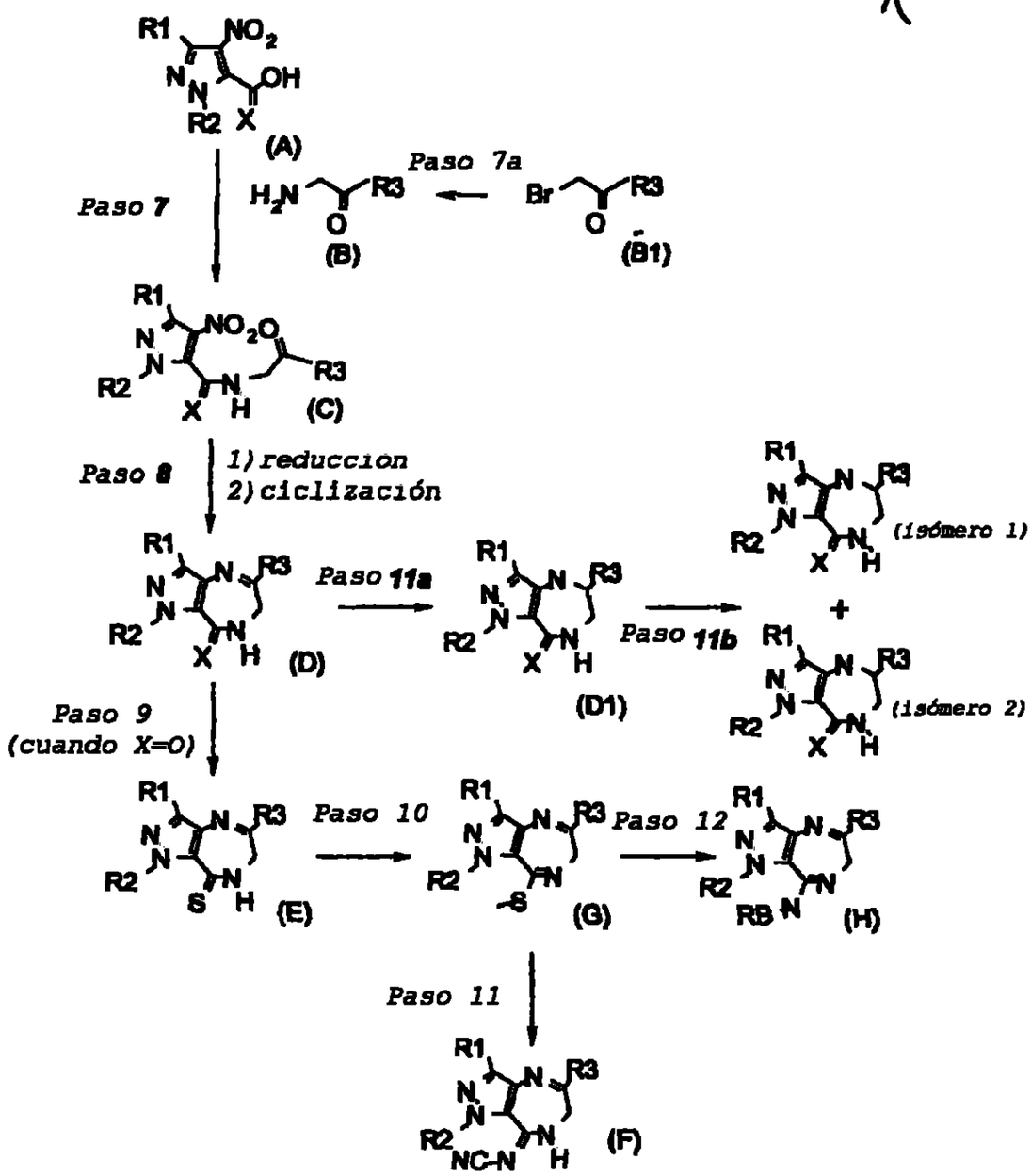
Esquema de reacción 1

En la descripción siguiente, cada uno de los pasos del esquema de reacción se describe en general Este proceso y sus diversos pasos se ejemplifican en el Ejemplo 1 Si un paso se puede realizar de acuerdo con diversos métodos (según los compuestos que se consideren), se lo describe (M1, M2,) e identifica con respecto a una referencia bibliográfica Los materiales iniciales se eligen en una forma apropiada (es posible que las funciones reactivas, si existieran, sean protegidas en una forma convencional)

Esquema de reacción 1



Esquema de reacción 1 (continuación)



Paso 1:

Una R_1-metil cetona en donde R_1 es uno de los sustituyentes del compuesto de la fórmula general I, reacciona con un dietil oxalato en la presencia de sodio para dar el compuesto de la fórmula A1

Paso 2

Luego se lleva a cabo una ciclización del compuesto A1, por ejemplo con un sulfato de hidrazina en la presencia de hidróxido de potasio para dar una mezcla del pirazol (A2) y el pirazol (A6) que comprenden cada uno el sustituyente R_1 Estos dos intermedios pueden separados y reaccionar posteriormente

Paso 3a

El Paso 3a es un paso alternativo del paso 9 que se describe a continuación Permite la introducción de un átomo de azufre en la posición del sustituyente X desde los primeros pasos de la síntesis, mediante la reacción de A2 o A6 con un reactivo adecuado, por ejemplo, el reactivo de Lawesson, para dar un compuesto de la fórmula A2a o A6a en donde X es igual a O o S y R_1 es lo definido anteriormente

Paso 3

El Paso 3 esencialmente comprende la nitración del núcleo de pirazol Esta nitración se realiza en los compuestos A2 A2a

A6, A8 o A9 y se puede realizar de acuerdo con 3 métodos descriptos en la bibliografía

- usando $NaNO_3/H_2SO_4$ (método M1), ver el Ejemplo 1, Aust J Chem , 47, 1009-1021, 1994,
- usando HNO_3/H_2SO_4 (método M2),
- o usando $Cu(NO_3)_2$ (método M3), J Org Chem , 46, 3056-3060, 1981

para dar un compuesto de la fórmula A, A3, A4, A5 o A7 en donde X es igual a O o S

Paso 4

En este paso, el compuesto A3 se esterifica Esto se puede realizar mediante la reacción del compuesto A3 con etanol en un medio ácido Se obtiene así el compuesto A4 en donde X es igual a O o S y R_1 es lo definido anteriormente

Paso 5

Los pirazoles A2, A4, A6 y A7 se alquilan de cuerdo con diversos métodos

- mediante la reacción de dimetil sulfato (para dar derivados con R_2 = etil) (método M4), J Med Chem , 16, 12, 1346-1354, 1973)

- mediante la reacción con un compuesto del tipo R_2-hal, en donde R_2 es lo definido para el compuesto de la fórmula general I y hal es un halógeno (método M5)

Se obtiene un compuesto de la fórmula A5, A8, o A9 en donde X es igual a O o S

Paso 6

Durante este paso, la función de éster (X = O) o la función de tioéster (X = S) se hidroliza, por ejemplo mediante la reacción del compuesto A5 con hidróxido de sodio Esto da el compuesto A en donde X es igual a O o S y R_1 y R_2 son lo definido anteriormente

Paso 7

Durante este paso, el compuesto A reacciona con el compuesto B de la fórmula general



en donde R_3 es uno de los sustituyentes del compuesto de la fórmula general I Preferentemente, se usa un clorhidrato del compuesto B Cuando éste no está comercialmente disponible, el producto (B) se sintetiza en un paso (paso 7a), empezando con

el compuesto (B1), que está comercialmente disponible o descripto en la bibliografía La sustitución nucleófila del bromo con la función de amina primaria se obtiene de acuerdo con diversos métodos

- Método de Delepine (método M6), J Heterocyclic Chem , 24, 297-301, 1987
- Método a través de la síntesis de una bisformamida (método M7), Tetrahedron Lett , 30, 39, 5285-58-286, 1889, Síntesis, 122-124, 1990

El compuesto C en donde X es igual a O o S se obtiene de acuerdo con diversos métodos de acoplamiento (paso 7)

- Método de acoplar N-hidroxisuccinimida y diciclohexilcarbodiimida (método M8, ver el ejemplo 1)
- Método de acoplar sobre un soporte sólido (método M9) el compuesto A (1 eq) reacciona con N-ciclohexilcarbodiimida y N'-metilpoliestireno HL (2 eq) en diclorometano Después de agitarse durante media hora, se agregan el compuesto B (1 eq) y trietilamina (1 eq) Después de 24 horas a temperatura ambiente, se agrega metil isocianato poliestireano HL Después de 2 horas, el medio de reacción se filtra y el filtrado se concentra para dar el compuesto C en donde X es igual a O o S
- Método de acoplar con EDCI clorhidrato de 1-(3-dimetilamino-propil)-3-etilcarbodiimida y HOBt (1-

hidroxibenzotriazol) (método M10) el compuesto B reacciona, con agitación, con el compuesto A en una cantidad equimolar en diclorometano en la presencia de un equivalente de trietilamina, un equivalente de 1-hidroxibenzotriazol y un equivalente de clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida Después de 24 horas a temperatura ambiente, el medio de reacción se lava con agua, la fase orgánica se seca y se evapora hasta secarse para dar el compuesto de la fórmula C en donde X es igual a O o S y R_1, R_2 y R_3 son lo definido anteriormente

Paso 8

Durante este paso, el compuesto C se cicliza de acuerdo con diversos métodos para dar el compuesto D en donde X es igual a O o S y R_1, R_2 y R_3 son lo definido anteriormente

- usando Fe/HCl (método M11) (ver el ejemplo 1)
- usando $SnCl_2$ (método M12) una amida del tipo C se disuelve en etanol con 5 equivalentes de dihidrato de cloruro de estaño El medio de reacción refluye durante 4 horas Después de enfriarse a temperatura ambiente, se agrega agua desmineralizada y, cuando está fría, la solución es llevada a pH básico con 30% de hidróxido de sodio Después de la extracción con CH_2Cl_2 y del secado

el medio se evapora hasta secarse para dar el compuesto del tipo D, que se purifica, si es necesario, sobre sílico o cristalización

Paso 9

El paso 9 se usa cuando se desea para obtener un compuesto de la fórmula I en donde X es S si, en el compuesto D, X es O Los compuestos de este tipo se obtienen mediante la reacción del compuesto D, en donde X es O, con un reactivo adecuado, que permite que se realice su tionación A modo de ejemplo, se puede usar un reactivo de Lawesson Se obtiene entonces un compuesto de la fórmula E en donde X es S

Pasos 10 y 11

Los pasos 10 y 11 se usan cuando se desea obtener un compuesto de la fórmula I en donde X es N-CN Los compuestos de este tipo se obtienen de acuerdo con diversos métodos

- método M13 mediante la reacción del compuesto E con hidruro de sodio y luego con yodometano para dar el compuesto (G) Este compuesto luego es puesto en contacto con cianamida y trietilamina para dar un compuesto del tipo (F), Heterociclos, 36, 777-783, 1993

- método M14 $Ph_3PSnN=C=NSnPPh_3$ en etanol, J Med Chem , 35, 12, 2327-2340, 1992

- método M15 cloruro de fosforilo, cianamida y trietilamina, Chem Pharm Bull , 42, 12, 2475-2482, 1994

- método M16 cianamida, trietilamda [sic], acetato de mercurio y acetonitrilo, Can J Chem , 63, 3089-3101, 1985

Pasos 11a y 11b

El Paso 11a permite reducir la función de imina del compuesto D mediante la reacción con un agente reductor, por ejemplo $NaBH_4$, en una mezcla polar, por ejemplo metanol/agua en la presencia de paladio sobre carbón para dar el racemato D1 en donde X es O o S y R_1, R_2 y R_3 son lo definido anteriormente, y el siguiente paso (11b) corresponde a la separación de los enantiómeros (isómero 1 e isómero 2), por ejemplo por medio de HPLC sobre una columna quiral de Diacel CD-H (250 mm x 4,6 mm, 5 µm, velocidad de flujo 1 ml/min , 80/20 heptano/isopropanol)

Estos pasos 11a y 11b, también corresponden en el caso de un compuesto de la fórmula D en donde X es N-CN o $N-R_8$

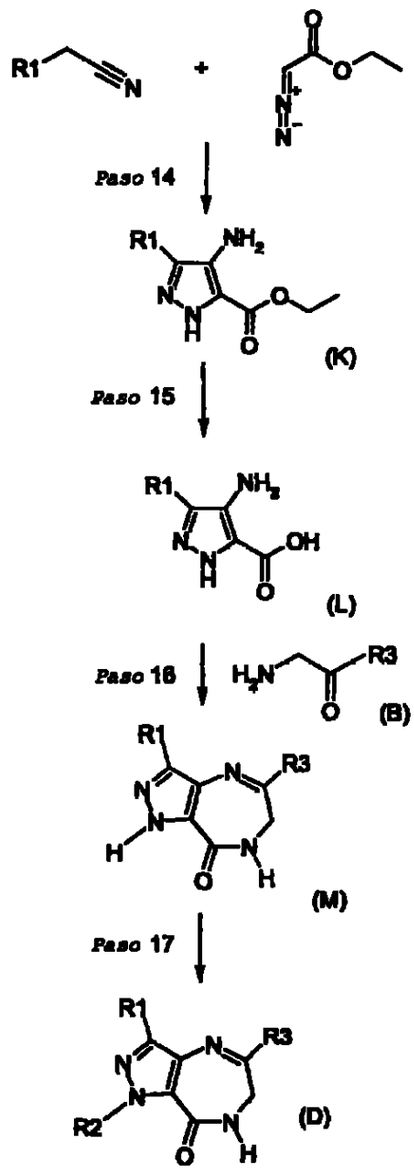
Pasos 10 y 12

Los pasos 10 y 12 se usan para obtener compuestos del tipo H El paso 10 permite la formación del derivado G y el paso 12 produce la introducción del grupo N-R_8 de acuerdo con un método inspirado por la bibliografía J Med Chem , 42, 2909-2919, 1999

Esquema de reacción 2

Este esquema de reacción deriva en la síntesis de los derivados D en donde X es O con R_1 = arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre y R_2 y R_3 son lo definido anteriormente Este proceso se ilustra con el Ejemplo 4

Esquema de reacción 2



Paso 14

La síntesis del pirazol se realiza en las condiciones descriptas en Farmaco Ed Sci , 39, 7, 1984, 618-636

Paso 15

Durante este paso, la función de éster del compuesto K se hidroliza, por ejemplo mediante la reacción del compuesto K con hidróxido de sodio Esto da el compuesto L

Paso 16

Este paso deriva en la formación del derivado M después del acoplamiento con el compuesto B y la ciclización

Paso 17

Este paso permite la formación de los compuestos D con x = O y R_1 = arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre y R_2 y R_3 son lo definido anteriormente

El compuesto M se alquila mediante la reacción con un compuesto del tipo R_2-hal, en donde R_2 es lo definido anteriormente para el compuesto de la fórmula general I y hal es un halógeno Se obtiene así el compuesto D

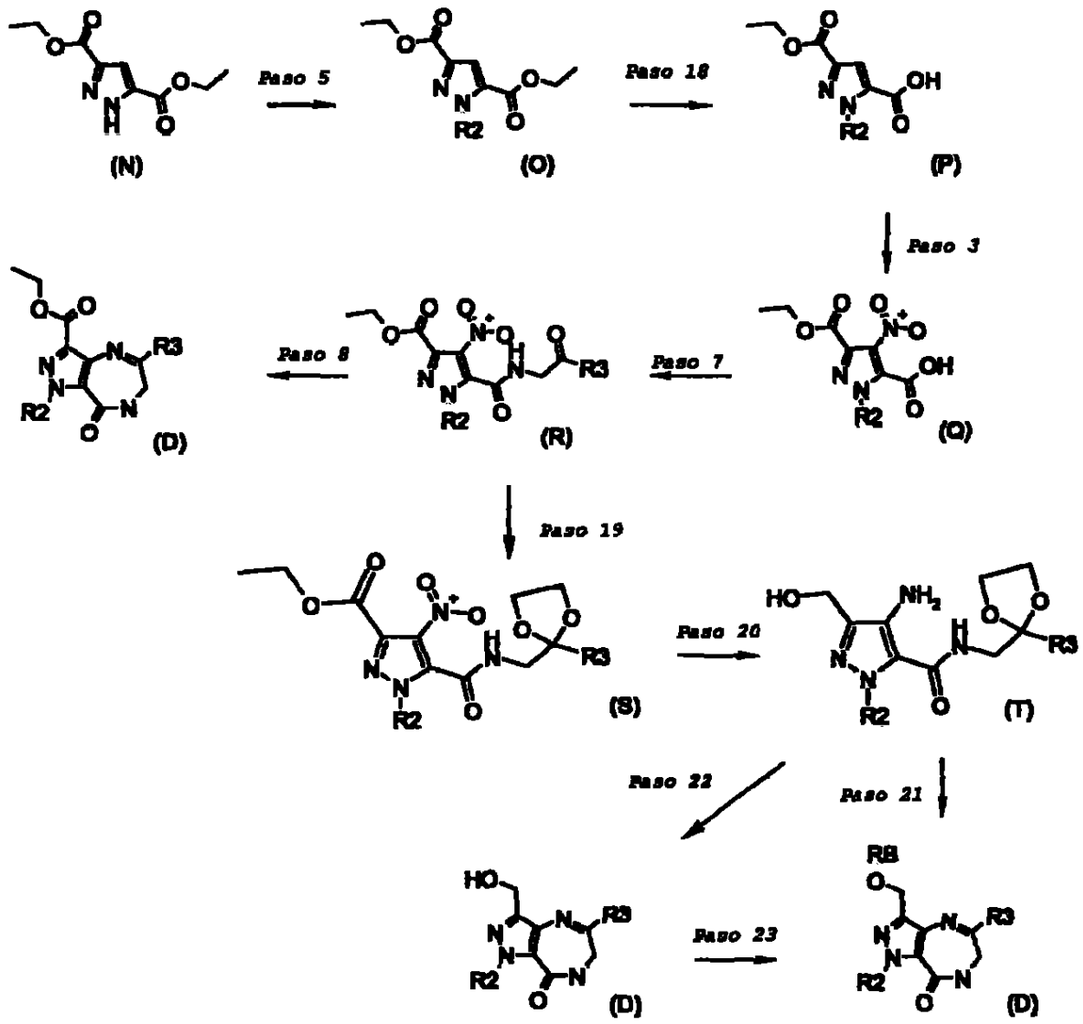
Esquema de reacción 3

Este esquema describe la síntesis de los compuestos D con R_1 = $(CH_2)_nOR_B$ o $(CH_2)_nCOOR_B$ Estas moléculas pueden derivar, mediante reacciones estándar de la química orgánica, en la formación de los compuestos D con R_1 = $(CH_2)_nC(O)R_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$ o $(CH_2)_nZ$ donde n, R_A, R_B, R_C y Z son lo descripto anteriormente

Los pasos 3, 5, 7 y 8 son los descriptos anteriormente en general

Los pasos 5, 18, 3, 7 y 8 se ilustran con el Ejemplo 5 y los pasos 19, 20 y 21 con el Ejemplo 97

Esquema de reacción 3



Paso 22

Este paso de ciclización se realiza en un medio ácido, por ejemplo 5% de HCl, en un solvente aprótico tal como tetrahidrofurano, para dar el derivado hidroxi D con R_1 = CH_2OH

Paso 23

Este paso deriva en la síntesis de diversos derivados D (R_1=OR_8) usando, por ejemplo, un compuesto del tipo R_8-hal en donde R_8 es lo definido anteriormente y hal es un halógeno

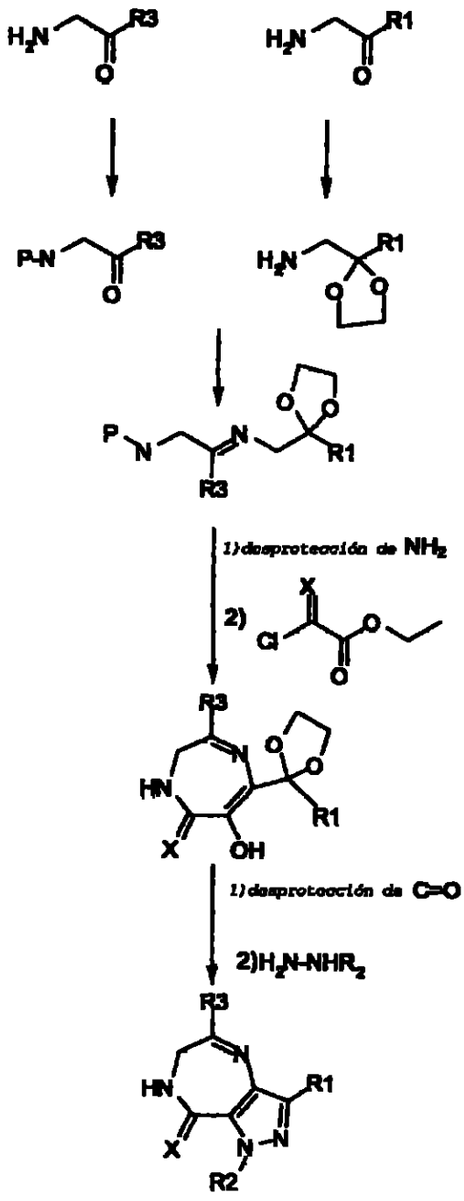
Paso 21

Este paso se limita al uso de solventes hidrolizados tales como MeOH y EtOH, durante el paso de ciclización del compuesto T, también permite la síntesis de los compuestos D con R_1=OR_8

Esquema de reacción 4

Éste es un método alternativo para sintetizar los compuestos de la fórmula general I en donde X es O o S y R_1, R_2 y R_3 son lo definido anteriormente Este método alternativo se ilustra en el esquema siguiente

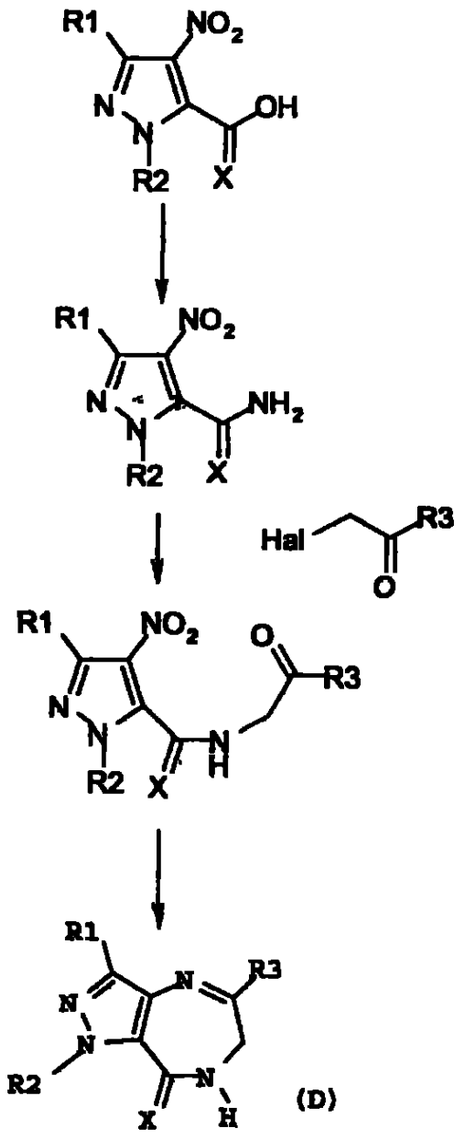
Esquema de reacción 4



Esquema de reacción 5

Éste es otro método para sintetizar compuestos de la fórmula general I en donde X es O o S Este método se ilustra en resumen en el esquema dado a continuación Una descripción más detallada de esta síntesis se presenta en la Patente Estadounidense 5 272 147, cuyo contenido se incorpora en la presente solicitud de patente como referencia

Esquema de reacción 5



(D)

EJEMPLOS

EJEMPLO 1

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = etilo, R_3 = fenilo)

Paso 1

0,37 g (0,0138 mol) de sodio se disuelve en porciones en 40 ml de etanol anhidro bajo nitrógeno a temperatura ambiente Se agrega 1,86 ml (13,6 mmol) de dietil oxalato en 10 ml de etanol anhidro Se agrega 1,47 ml (13,6 mmol) de isopropil metil cetona La mezcla de la reacción se deja en agitación toda la noche a temperatura ambiente (RT) y luego se evapora hasta secarse El producto obtenido se aísla en la forma de un polvo de color naranja (compuesto A1) m = 3,1 g (100%)

MS (ES+), m/z = 185

Rf (CH_2Cl_2/acetona 90/10) = 0,91

Paso 2

0,98 g (14,8 mmol) de hidróxido de potasio se disuelve en 7,5 ml de agua y el medio de reacción se enfrió a 0°C Se agregan 3,1 g (14,8 mmol) en porciones del compuesto A1 (ver el esquema 1) y la mezcla se agita durante 30 minutos a 0°C Se agrega 1 94 g (14 8 mmol) de sulfato de hidrazina y la mezcla

luego se agita durante 45 minutos a 0°C Después de la filtración, el precipitado se enjuaga con una pequeña cantidad de agua y luego se seca para dar 0,93 g (13%) de un polvo blanco (compuesto A2)

^{1}H NMR (DMSO, 400 MHz)

1,2 ppm (6H, d) 2,95 ppm (1H, m), 6,45 ppm (1H, s) 12,3 ppm (1H, m)

Paso 3

Se usa el método M1 Se introducen 100 ml de H_2SO_4 en un matraz de base circular El matraz se enfría a 0°C y se agregan 10,09 g (0,065 mol) del compuesto A2 (ver el esquema 1)(0,065 mol), luego se agregan 16,5 g (0,195 mol) de $NaNO_3$ La mezcla se calienta a temperatura ambiente y se agita durante 24 horas El medio de reacción se vierte suavemente en 200 ml de agua helada, enfriando el matraz si es necesario, y se agita durante 30 minutos El precipitado se filtra y se enjuaga con agua Después de secar, se obtienen 4,25 g (33%) de un polvo blanco (compuesto A3)

MS (ES-) m/z= 198

^{1}H NMR (DMSO, 400 MHz)

1,3 ppm (6H, d, 3,5 ppm (1H, m) 13,9 ppm (2H, m)

MS (ES+), m/z = 256

^{1}H NMR ($CDCl_3$, 400 MHz)

1,3 ppm (6H, d) 1,35 ppm (3H, t) 1,45 ppm (3H, t) 3,45 ppm (1H, m), 4,2 ppm (2H, q) 4,45 ppm (2H, q)

Paso 6

Se introducen 2,92 g (0,011 mol) del compuesto A5 (ver el esquema 1) en 15 ml de metanol en un matraz de base circular, luego se agrega una solución de 0,68 g (0,0165 mol) de hidróxido de sodio en 15 ml de agua La mezcla se agita a temperatura ambiente durante 3 h Después de evaporar el metanol, el residuo se recoge en CH_2Cl_2, se agrega un volumen idéntico de agua y la mezcla resultante se acidifica (con agitación) con HCl concentrado (36%) Después de la separación de las fases mediante reposo, la fase orgánica se seca sobre Na_2SO_4 y se concentra para dar 2,3 g de un polvo blanco (92%) (compuesto A)

MS (ES-), m/z = 226

^{1}H NMR (DMSO, 400 MHz)

1,2 ppm (6H, d), 1,35 ppm (3H, t), 3,35 ppm (1H, m) 4,15 ppm (2H, q)

Paso 7

Se usa el método M8 Se disuelve 1 g (4 mmol) del compuesto A (ver el esquema 1) en una mezcla de 25 7 ml de THF y 1 4 ml de

DMF, luego se agrega, bajo nitrógeno 0,51 g (4 mmol) de N-hidroxisuccinimida El medio de reacción se enfría a 0°C de manera de agregar en porciones 0,91 g (4 mmol) de diciclohexilcarbodiimida La mezcla se agita toda la noche a temperatura ambiente El precipitado formado se filtra y el filtrado se evapora hasta secarse El residuo se recoge en 20 ml de CH_2Cl_2, se agrega 0,75 g (4 mmol) de clohidrato de 2-aminoacetofenona bajo nitrógeno, el medio de reacción se enfría a 0°C, luego se agrega 0,61 ml (4 mmol) de trietilamina y la mezcla se agita a temperatura ambiente durante 3 horas El medio de reacción se vierte en agua con agitación Después de la extracción con diclorometano, el lavado con agua y el secado bajo Na_2SO_4, la fase orgánica se evapora hasta secarse para dar 1,3 g (86%) de un polvo blanco (compuesto C)

MS (ES+), m/z = 345

^1H NMR ($CDCl_3$, 400 MHz)

1,35 ppm (6H, d), 1,5 ppm (3H, q), 3,55 ppm (1H, m), 4,3 ppm (2H, q), 5 ppm (2H, d) 7,5 ppm (2H, t) 7,65 ppm (1H, d), 7,7 ppm (1H, m), 8 ppm (2H, d)

Paso 8

Se usa el método M11 SE introduce 1,3 g (3,7 mmol) del compuesto C (ver el esquema 1) en una mezcla de 30 ml de etanol y 7 ml de agua en un matraz de base circular, luego se agregan 2,2 g (3,9 mmol) de hierro y 0,5 ml de HCl concentrado

(36%) El medio de reacción refluye durante 1 h 15 minutos El hierro se remueve mediante filtración El filtrado se concentra hasta secarse y el residuo se recoge en CH_2Cl_2 y se lava dos veces con 70 ml de agua y luego con una solución de NaCl saturado, la fase orgánica se seca sobre Na_2SO_4, se filtra y se concentra para dar un polvo rojo amorfo (m = 0,9 g)

Este producto crudo se purifica mediante cromatografía rápida usando el siguiente gradiente de elución 98/2 de CH_2Cl_2/acetona hasta 90/10 de CH_2Cl_2/acetona

El polvo rojo obtenido después de la evaporación se recoge en la cantidad mínima de dietil éter y luego se filtra Después de secar, se aíslan 0,35 g (32%) de un polvo beige (compuesto D)

MS (ES+), m/z = 297

punto de fusión = 157,2°C

^1H NMR ($CDCl_3$, 40 MHz)

1,4 ppm (6H, d) 1,5 ppm (3H, t), 3,35 ppm (1H, m), 4,1 ppm (2H, d), 4,55 ppm (2H, q), 6,25 ppm (1H, m), 7,45 ppm (3H, m), 8,0 ppm (2H, m)

EJEMPLO 2

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = isopropilo, R_2 = etilo, R_3 = fenilo)

Paso 9

Se disuelven 0,2 g (0,67 mmol) del compuesto D (ver el esquema 1) en 7 ml de tolueno sobre tamices, y se agrega 0,54 g (1,34 mmol) de reactivo de Lawesson, bajo nitrógeno La mezcla se refluye durante 16,5 h El medio de reacción se enfría a temperatura ambiente, se agregan 2 ml de 5% de HCl, luego 25 ml de metanol y 25 ml de ciclohexano, la mezcla se agita, el precipitado se filtra y se deja que las dos fases se separen mediante reposo La fase de metanol se evapora El residuo se recoge en acetato de etilo y se lava con agua, la fase orgánica se seca sobre Na_2SO_4, se filtra y se evapora

El producto crudo se purifica mediante cromatografía rápida (80/20 de ciclohexano/acetato de etilo) Después de la evaporación, se obtiene 0,15 g (75%) de un polvo amarillo (compuesto E)

MS (ES+), m/z = 313

punto de fusión =164°C

^{1}H NMR ($CDCl_3$, 400 MHz)

1,4 ppm (6H, d) 1,5 ppm (3H, t), 3,3 ppm (1H, m), 4,2 ppm (2H, m), 4,8 ppm (2H, q) 7,45 ppm (3H, m), 8 ppm (2H, d) 8,3 ppm (1H, m)

EJEMPLO 3

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

(R_1 = isopropilo, R_2 = etilo R_3 = fenilo)

Paso 10

De acuerdo con M13, 1,83 g (5,86 mmol) de 1-etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona reaccionan con 0,18 g de 80% de hidruro de sodio en THF en reflujo durante 1 hora, y luego se agrega 0,44 ml de yoduro de metilo a temperatura ambiente La mezcla se refluye durante 2 horas para dar 1,53 g (80%) del metilsulfanilo del tipo G esperado (ver el Esquema 1)

punto de fusión = 98°C

MS (ES+), m/z = 327

^{1}H NMR (DMSO, 400 MHz)

8,1 ppm (2H, d) 7,4 ppm (3H, m) 4,4 ppm (4H, m) 3,2 ppm (1H, m), 2,4 ppm (3H, s), 1,4 ppm (3H, t) 1,3 ppm (6H, m)

Paso 11

0,5 g (1,53 mmol) del metilsulfanilo G reacciona con 0,12 g (2 eq) de cianamida para dar 0,396 g (81%) del producto del tipo F esperado (ver el Esquema 1)

punto de fusión = 222°C

MS (ES+), m/z = 321

^{1}H NMR (DMSO, 400 MHz)

9,4 ppm (1H, 1s) 8 ppm (2H, m) 7,4 ppm (3H, m) 4,3 ppm (2H, g), 4,1 ppm (2H, 1s), 3,1 ppm (1H, m), 1,3 ppm (3H, t), 1,2 ppm (6H, d)

EJEMPLO 4

1-Etil-3,5-difenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(R_1 = fenilo, R_2 = etilo, R_3 = fenilo)

Paso 15

35,75 g (0,15 mol) del compuesto K (ver el esquema 2) en 35 ml de metanol se introducen en un matraz de base circular, luego se agrega una solución de 9,24 g (0,231 mol) de hidróxido de sodio en 140 ml de agua La mezcla se agita a temperatura ambiente toda la noche Después de la evaporación, el residuo se recoge en etanol y luego se filtra y se seca para dar 26,7 g (87%) de un polvo beige (compuesto L, ver el esquema 1)

MS (ES+), m/z = 203,9

^{1}H NMR (DMSO, 400 MHz)

4,7 ppm (1H, m) 7,2 ppm (1H, m) 7,3 ppm (2H, t), 7,75 ppm (2H, d), 12,2 ppm (1H, m)

Paso 16

1,5 g (8,7 mmol) de clorhidrato de 2-aminoacetofenona se disuelven en una mezcla de 50 ml de THF y 10 ml de DMF luego

se agregan 1,22 ml (8,7 mmol) de trietilamina, 1,34 g (8,7 mmol) de hidrato de 1-hidroxibenzotriazol y luego 1,77 g (8,7 mmol) del compuesto L (ver el esquema 2) y finalmente 1,37 g (8,7 mmol) de 1-(3-dimetilaminopropil)-3-etilcarbodiimida La mezcla se calienta a 60°C durante 24 h El precipitado formado se filtra y el filtrado se recoge en agua Después de la extracción con acetato de etilo, los extractos se lavan con agua y se secan sobre Na_2SO_4 La fase orgánica se evapora hasta secarse para dar 1,8 g de un polvo naranja Este producto crudo se purifica usando el siguiente gradiente de elución desde CH_2Cl_2 hasta 95/5 CH_2Cl_2/metanol para dar 0,45 g(16%) de un polvo beige (compuesto M, ver el esquema 2)

MS (ES+), m/z = 303

^1H NMR (DMSO, 400 MHz)

4,15 ppm (2H, m), 7,3-7,55 ppm (6H, m), 8-8,1 ppm (4H, m), 8,3 ppm (1H, m) 14 ppm (1H, m)

Paso 17

De acuerdo con M5, 1,23 g (8,9 mmol) de K_2CO_3 se agregan, bajo una corriente de nitrógeno, a una solución de 2,7 g (8,9 mmol) del compuesto M (ver el esquema 2) en 30 ml de DMF anhidro, luego se agrega 0,71 ml (8,9 mmol) de yodoetano El medio de reacción se calienta a 60°C toda la noche El medio de reacción se extrae con éter dietílico y los extractos se secan

sobre Na_2SO_4, se filtran y luego se concentran para dar 3,6 g de un compuesto aceitoso

Este producto crudo se purifica usando el siguiente gradiente de elución desde CH_2Cl_2 hasta 98/2 de CH_2Cl_2/acetona El producto aceitoso así obtenido se cristaliza desde éter dietílico para dar 0,2 g (7%) de un polvo amarillo (compuesto (ver el esquema 2))

MS (ES+), m/z = 331

^1H NMR (DMSO, 400 MHz)

1,4 ppm (3H, t), 4,1 ppm (2H, m), 4,5 ppm (2H, q), 7,3 ppm (1H, m), 7,4 ppm (2H, m), 7,5 ppm (3H, m), 8 ppm (4H, m), 8,5 ppm (1H, m)

EJEMPLO 5

Etil 1-etil-8-oxo-5-fenil-1,6,7,8-tetrahidropirazolo-[4,3-e][1,4]diazepin-3-carboxilato

(R_1 = carboxilato de etilo R_2 = etilo, R_3 = fenilo)

Paso 5

20 g (94 mmol) de dietil 3,5-pirazoldicarboxilato (comercial) reaccionan con 8,3 ml (103 mmol) de yodoetano para dar 21,4 g (95%) de un pirazol O (ver el esquema 3)

Rf (95/5 de CH_2Cl_2/MeOH) = 0,70

MS (ES+), m/z = 240,8

^1H NMR (CDCl 400 MHz)

102

89.

7,25 ppm (1H, s), 4,6 ppm (2H, q), 4,25-4,4 ppm (14H, m), 1,4 ppm (3h, t), 1,3 ppm (6H, m)

Paso 18

21 g (87 mmol) del pirazol O (ver el esquema 3) reaccionan en condiciones en frío, en 100 ml de agua y 160 ml de THF con una solución de 3,84 g (96 mmol) de pelotillas de hidróxido de sodio en 100 ml de agua Después de calentar a temperatura ambiente, la mezcla de reacción se agita durante 2 horas La mezcla luego se extrae con éter dietílico La fase acuosa se acidifica con 36% de HCl bajando a pH = 2 y luego se extrae con diclorometano La fase orgánica se seca sobre Na_2SO_4 y luego se filtra y se concentra para dar 13,5 g (73%) del compuesto P (ver el esquema 3)

Rf (80/20 de CH_2Cl_2/MeOH) = 0,5

MS (ES+), m/z = 212,8

^{1}H NMR ($CDCl_3$, 400 MHz)

9,1-9,5 ppm (1H, m), 7,4 ppm (1H, s) 4,65 ppm (2H, q) 4,35 ppm (2H, q), 1,4 ppm (3H, t) 1,3 ppm (3H, t)

Paso 3

De acuerdo con M3, 6 g (28 mmol) del compuesto P (ver el esquema 3) reaccionaron con 19,75 g (84 mmol) de nitrato de cobre hemipentahidratado en una mezcla de anhídrido

trifluoroacético y cloroformo, para dar 6,9 g (95%) del compuesto Q (ver el esquema 3)

Rf (80/20 de CH_2Cl_2/MeOH + 0,3% de HCOOH) = 0,46

MS (ES^-), m/z = 255,8

^1H NMR (DMSO, 400 MHz)

4,55 ppm (2H, q), 4,3 ppm (2H, q), 1,4 ppm (3H, t), 1,3 ppm (3H, t)

Paso 7

De acuerdo con M8, 3 g (11,7 mmol) del compuesto Q (ver el esquema 3) reaccionan con 2 g (11,7 mmol) de clorhidrato de 2-amonoacetofenona para dar 4,38 g del compuesto R (ver el esquema 3)

MS (ES+), m/z = 372,8

^1H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (3h, m), 7,5 ppm (1H, m), 7,45 ppm (2H, m), 4,9 ppm (2H, d), 4,3-4,5 ppm (4H, m) 1,45 ppm (3H, t) 1,35 ppm (3H, t)

Paso 8

De acuerdo con M11, 1 g (2,7 mmol) del compuesto R (ver el esquema 3) se refluye con 0,3 g (5,4 mmol) de hierro y 0,27 ml de 36% de HCl en una mezcla de etanol y agua para dar 0,1 g (12%) del compuesto D esperado (ver el esquema 3)

Rf (50/50 de ciclohexano/EtOAc) = 0,19

104

101

SM (ES^+), m/z = 327

1H NMR ($CDCl_3$, 400 MHz)

8,55 ppm (1H, m) 8,05 ppm (2H, m) 7,55 ppm (3H, m) 4,55 ppm (2H, q), 4,3 ppm (2H, q) 4,1 ppm (2H, d), 1,4 ppm (3h, t) 1,3 ppm (3H, t)

EJEMPLO 6

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo R_2 = etilo, R_3 = 4-metoxifenilo)

Paso 7

De acuerdo con M8, 0,5 g (2,5 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico (ver J Med Chem , 16, 1973, 1346-1354 o la Patente Estadounidense 3 700 657) reacciona con 0,5 g de clorhidrato de 2-amino-4'-metoxiacetofenona para dar 0,78 g (90%) de una amida del tipo C (ver el esquema 1)

punto de fusión 131,5°C

Análisis calculado para $C_{16}H_{18}N_4O_5$

C, 55,49, H, 5,24, N, 16,11, O, 23,10

hallado C, 55,45 H, 5,44, N, 16,09, O, 22,9

Paso 8

De acuerdo con M11, 0,6 g (1,73 mmol) de la amida C (ver el esquema 1) se refluye con 1,04 g de hierro y 0,173 ml de 36%

de HCl en una mezcla de etanol/agua para dar 0,35 g (70%) del producto D esperado (ver el esquema 1)

punto de fusión 178°C

MS (ES^+), m/z = 299

^1H NMR ($CDCl_3$, 400 MHz)

7,8 ppm (2H, d) 6,9 ppm (2H, d) 6,0 ppm (1H, t) 4,5 ppm (2H, q), 4,2 ppm (2H, d), 3,8 ppm (3H, s), 2,4 ppm (3H, s), 1,45 ppm (3H, t)

EJEMPLO 7

5-(4-Bromofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 4-bromofenilo)

Paso 7

De acuerdo con M8, 0,5 g (2,5 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,51 g de clorhidrato de 2-amino-4'-bromoacetofenona para dar 0,57 g (60%) de una amida del tipo C (ver el esquema 1)

punto de fusión 184°C

^1H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (1H, s), 7,8 ppm (2H, d), 7,6 ppm (2H, d), 4,9 ppm (2H, s) 4,3 ppm (2H, q), 2,5 ppm (3H, s) 1,5 ppm (3H, t)

Análisis calculado para $C_{15}H_{15}BrN_4O_4$

C 45 59 H 3 83 Br 20 22 N 14 18 O 16 19

Hallado C, 45,42, H, 3,74, Br, 19,99, N, 14,11, O, 16,22

Paso 8

De acuerdo con M11, 0,475 g (1,2 mmol) de la amida C (ver el esquema 1) se refluye con 0,721 g de hierro y 0,12 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,25 g (60%) del producto D extraído (ver el esquema 1)

punto de fusión 223°C

MS (ES^+), m/z = 348

^1H NMR ($CDCl_3$, 40 MHz)

7,8 ppm (2H, d), 7,5 ppm (2H, d), 6,2 ppm (1H, s), 4,5 ppm (2H, q), 4,0 ppm (2H, s), 2,3 ppm (3H, s), 1,4 ppm (3H, t)

EJEMPLO 8

1-Etil-3-metil-5-naft-2-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = naftilo)

Paso 7

De acuerdo con M8, 0,45 g (2,25 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,5 g clorhidrato de 2-amino-1-naft-2-il-etanona para dar 0,588 g (75%) de una amida del tipo C (ver el esquema 1)

Rf (5/5 de ciclohexano/EtOAc) = 0,25

^1H NMR ($CDCl_3$, 400 MHz)

8,6 ppm (1H, t), 8,0 ppm (7H, m), 5,15 ppm (2H, d), 4,4 ppm (2H, q), 2,6 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

0,58 g (1,58 mmol) de la amida C (ver el esquema 1) se refluye con 0,948 g de hierro y 0,158 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,32 g (79%) del producto D esperado (ver el esquema 1)

punto de fusión 193°C

MS (ES^+), m/z = 319

^1H NMR ($CDCl_3$, 400 MHz)

8,2 ppm (2H, m), 7,8 ppm (3H, m), 7,5 ppm (2H, m), 6,4 ppm (1h, t), 4,5 ppm (2H, q), 4,2 ppm (2H, d), 2,4 ppm (3H, s), 1,45 ppm (3H, t)

EJEMPLO 9

5-(3-Clorotien-2-il)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo R_2 = etilo, R_3 = clorotienilo)

Paso 7

De acuerdo con M8, 0,235 g (1,18 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,5 g de clorhidrato de 2-amino-1-(3-clorotien-2-il)etanona para dar

0,32 g (76%) de una amida del tipo C (ver el esquema 1) en donde R_1, R_2 y R_3 son lo definido en este ejemplo

Rf (5/5 de ciclohexano/EtOAc) = 0,53

^{1}H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (1H, m), 7,7 ppm (1H, d), 7,1 ppm (1h, d), 5,0 ppm (2H, d) 4,45 ppm (2H, q) 2,6 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,31 g (0,87 mmol) de la amida C (ver el esquema 1) se refluye con 0,52 g de hierro y 0,087 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,135 g (50%) del producto D esperado (ver el esquema 1)

punto de fusión 213°C

MS (ES^+), m/z = 309

^{1}H NMR ($CDCl_3$, 400 MHz)

7,4 ppm (1H, d), 6,9 ppm (1H, d), 6,1 ppm (1H, t), 4,55 ppm (2H, q), 4,3 ppm (2H, d) 2,4 ppm (3H,s), 1,45 ppm (3H, t)

EJEMPLO 10

Metil 3-(1-etil-3-metil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)propanoato

(R_1 = metilo, R_2 = etilo, R_3 = propanoato de metilo)

Paso 7

106 / 46

De acuerdo con M8, 0,44 g (2,21 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico con 0,41 g (1 eq) de clorhidrato de metil 5-amino-4-oxopentanoato para dar 0,63 g (87%) de una amida del tipo C (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/metanol) = 0,48

^1H NMR ($CDCl_3$, 400 MHz)

7,7 ppm (1H, m), 4,4 ppm (2H, d), 4,3 ppm (2H, q), 3,7 ppm (3h, s), 2,85 ppm (2H, dd) 2,7 ppm (2H, dd), 2,5 ppm (3H, s) 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,6 g (1,83 mmol) de la amida C (ver el esquema 1) se refluye con 1,1 g de hierro y 0,18 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,42 g (83%) del producto D esperado (ver el esquema 1)

punto de fusión 68°C

^1H NMR ($CDCl_3$, 400 MHz)

6,7 ppm (1H, t) 4,5 ppm (2h, q) 3,8 ppm (3H, s) 3,55 ppm (2H, d), 2,85 ppm (2H, t), 2,7 ppm (2H, t), 2,2 ppm (3H, s), 1,45 ppm (3H, t)

EJEMPLO 11

5-(4-Clorofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

R_1 = metilo R_2 = etilo R_3 = 4-clorofenilo

Paso 7

De acuerdo con M8, 0,5 g (2,5 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,517 g (1 eq) de clorhidrato de 2-amino-4'-cloroacetofenona para dar 0,5 g (57%) de una amida del tipo C (ver el esquema 1) en donde R_1, R_2 y R_3 son lo definido en este ejemplo Rf (5/5 de ciclohexano/EtOAc) = 0,55

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (3H, d), 7,5 ppm (2H, d), 4,95 ppm (2H, d), 4,35 ppm (2H, q), 2,5 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,45 g (1,28 mmol) de la amida C (ver el esquema 1) se refluye con 0,7 g de hierro y 0,128 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,27 g (70%) del producto D esperado (ver el esquema 1)

punto de fusión 215°C

MS (ES^+), m/z = 303

^{1}H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (2H, d), 7,5 ppm (2H, d), 6 ppm (1H, t), 4,5 ppm (2H, q), 4,1 ppm (2H, d), 2,4 ppm (3H, s), 1,45 ppm (3H, t)

EJEMPLO 12

5-(4-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 4-aminofenilo)

Paso 7

De acuerdo con M8, 0,5 g (2,5 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,540 g (1 eq) de clorhidrato de 2-amino-4'-nitroacetofenona para dar 0,45 g (50%) de una amida del tipo C (ver el esquema 1)

Rf (EtOAc) = 0,9

^{1}H NMR ($CDCl_3$, 400 MHz)

8,4 ppm (2H, d), 8,2 ppm (2H, d), 8,0 ppm (1H, m), 5,0 ppm (2H, d), 4,4 ppm (2H, q), 2,5 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,38 g (1,05 mmol) de la amida C (ver el esquema 1) se refluye con 0,63 g de hierro y 0,105 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,12 g (40%) del producto D esperado (ver el esquema 1)

punto de fusión 212°C

MS (ES^+), m/z = 284

^{1}H NMR ($CDCl_3$, 400 MHz)

8,2 ppm (1H, t), 7,8 ppm (2H, d), 6,6 ppm (1H, d), 5,8 ppm (2H, s), 4,5 ppm (2H, q), 3,9 ppm (2H, d), 2,3 ppm (3H, s), 1,45 ppm (3H, t)

109 1/2

EJEMPLO 13

1-Etil-5-(4-fluorofenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 4-flurofenilo)

Paso 7

De acuerdo con M8, 0,1 g (0,53 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,1 g de clorhidrato de 2-amino-4'-fluoroacetofenona para dar 0,17 g (96%) de una amida del tipo C (ver el esquema 1)

Rf (5/5 ciclohexano/EtOAc) = 0,45

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, m), 7,9 ppm (1H, m), 7,15 ppm (2H, m), 4,95 ppm (2H, d), 4,3 ppm (2H, q), 2,5 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,16 g (0,48 mmol) de la amida C (ver el esquema 1) se refluye con 0,287 g de hierro y 0,048 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,08 g del producto D esperado (ver el esquema 1)

punto de fusión 174°C

MS (ES^+), m/z = 287

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, m) 7,15 ppm (2H, m), 6,7 ppm (1H, t), 4,5 ppm (2H, q) 4,1 ppm (2H, d) 2,4 ppm (3H, s) 1,5 ppm (3H, t)

10 113

EJEMPLO 14

5-(3-Bromofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 3-bromofenilo)

Paso 7

De acuerdo con M8, 0,08 g (0,4 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,1 g (1 eq) de clorhidrato de 2-amino-4'-bromoacetofenona para dar 0,16 g (100%) de una amida del tipo C (ver el esquema 1)

Rf (98/2 de CH_2Cl_2/MeOH) = 0,29

^{1}H NMR ($CDCl_3$, 400 MHz)

8,15 ppm (1H, s), 7,9 ppm (2H, m), 7,8 ppm (1H, m), 7,4 ppm (1H, m), 5,0 ppm (2H, d), 4,3 ppm (2H, q) 2,6 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,16 g (0,4 mmol) de la amida C (ver el esquema 1) se refluye con 0,24 g de hierro y 0,04 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,06 g (43%) del producto D esperado (ver el esquema 1)

punto de fusión 173°C

MS (ES^+), m/z = 348

^{1}H NMR ($CDCl_3$, 400 MHz)

8,1 ppm (1H, m), 7,9 ppm (1H, m), 7,6 ppm (1H, m), 7,4 ppm (1H, m), 7,25 ppm (1H, s), 6,3 ppm (1H, t), 4,6 ppm (2H, q), 4,1 ppm (2H, d), 2,4 ppm (3H, s), 1,5 ppm (3H, t)

EJEMPLO 15

3-Metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo-[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = propilo, R_3 = fenilo)

Paso 7

De acuerdo con M8, 0,37 g (1,6 mmol) de ácido 5-metil-4-nitro-2-propil-2H-pirazol-3-carboxílico reacciona con 0,28 g (1,6 mmol) de clorhidrato de 2-aminoacetofenona para dar 0,54 g (96%) de una amida del tipo C (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,7

^1H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, d), 7,85 ppm (1H, t), 7,65 ppm (1H, m), 7,55 ppm (2H, m), 5,0 ppm (2H, d), 4,25 ppm (2H, t), 2,55 ppm (3H, s) 1,9 ppm (2H, m), 0,9 (3H, t)

Paso 8

De acuerdo con M11, 0,138 g (0,42 mmol) de la amida C (ver el esquema 1) se refluye con 0,28 g de hierro y 0,05 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,072 g (61%) del producto D esperado (ver el esquema 1)

punto de fusión 171°C

MS (ES^+), m/z = 283

^1H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, d), 7,5 ppm (3H, m), 6,65 ppm (1H, t), 4,5 ppm (2H, t), 4,15 ppm (2H, d), 2,4 ppm (3H, s), 1,9 ppm (2H, m), 0,9 ppm (3H, t)

EJEMPLO 16

1-(2-Hidroxietil)-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = 2-hidroxietilo, R_3 = fenilo)

Paso 5

6,3 g (33,8 mmol) de un pirazol del tipo A4 (ver el esquema 1) y J Org Chem , 21, 833-835, 1956, Gazz Chim Ital , 75, 121-131, 1945) reaccionan con 8,48 g (40,5 mmol) de 2-(2-bromoetoxi)tetrahidro-2H-pirano (comercial) para dar 3,44 g (31%) de un pirazol A5 (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/acetona) = 0,47

^1H NMR ($CDCl_3$, 400 MHz)

4,55-4,35 ppm (5H, m), 4,0 ppm (1H, m), 3,7-3,4 ppm (3H, m), 2,5 ppm (3H, s), 1,8-1,55 ppm (6H, m), 1,5 ppm (3H, t)

Paso 6

1,1 g (3,4 mmol) del pirazol A5 (ver el esquema 1) reacciona con 0,2 g (5,1 mmol) de hidróxido de sodio en una mezcla de

113 116

metanol y agua para dar 0,97 g (95%) de un pirazol del tipo A (ver el esquema 1)

Rf (80/20 de CH_2Cl_2/MeOH) = 0,26

^1H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (1H, s), 4,7-4,5 ppm (3H, m), 4,0 ppm (1H, m), 3,8-3,45 ppm (3H, m), 2,5 ppm (3H, s), 1,9-1,4 ppm (6H, m)

Paso 7

De acuerdo con M8, 0,9 g (3 mmol) de ácido 2-(2-hidroxietil)-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,52 g (3 mmol) de clorhidrato de 2-aminoacetofenona para dar 1,43 g (100%, crudo) de una amida del tipo C (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,51

^1H NMR ($CDCl_3$, 400 MHz)

8,3 ppm (1H, s) 8,0 ppm (2H, m) 7,6 ppm (1H, m), 7,5 ppm (2H, m), 4,7 ppm (1H, m), 4,5 ppm (2H, t), 4,1 ppm (1H, m), 3,85 ppm (1H, m), 3,7-3,4 ppm (2H, m), 2,55 ppm (3H, s), 1,9-1,4 ppm (6H, m)

Paso 8

De acuerdo con M11, 1,4 g (3 mmol) de la amida C (ver el esquema 1) se refluye con 1,8 g de hierro y 0,31 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,09 g (11%) del producto D esperado (ver el esquema 1)

punto de fusión 75°C

114

MS (ES^+), m/z = 285

^1H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, m), 7,55 ppm (3H, m), 7,05 ppm (1H, t), 4,65 ppm (2H, t), 4,15 ppm (2H, d), 4,0 ppm (2H, m), 3,9 ppm (1H, OH), 2,4 ppm (3H, s)

EJEMPLO 17

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = metilo, R_2 = etilo, R_3 = fenilo)

Paso 9

0,2 g (0,74 mmol) de una pirazolodiazepina del tipo D (ver el esquema 1), en donde R_1, R_2 y R_3 son lo definido en este ejemplo, se refluye en tolueno con 0,6 g (2 eq) del reactivo de Lawesson para dar 188 mg (89%) del producto E esperado (ver el esquema 1)

punto de fusión 203,5°C

MS (ES^+), m/z = 285

^1H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, m), 7,8 ppm (1H, t), 7,5 ppm (3H, m), 4,8 ppm (2H, q) 4,25 ppm (2H, d), 2,5 ppm (3H, s), 1,6 ppm (3H, t)

EJEMPLO 18

1-Etil-5-(3-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

118

115

(R_1 = metilo, R_2 = etilo, R_3 = 3-metoxifenilo)

Paso 7

De acuerdo con M8, 0,5 g (2,51 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,51 g (2,51 mmol) de clorhidrato de 2-amino-3'-metoxiacetofenona (Patent, Brachwitz, Werner, DD65929, 1967) para dar 0,8 g (92%) de una amida del tipo C (ver el esquema 1)

Rf (CH_2Cl_2/MeOH 90/10) = 0,87

^{1}H NMR ($CDCl_3$, 400 MHz)

7,95 ppm (1H, s), 7,55 ppm (1H, m) 7,5 ppm (1H, m), 7,4 ppm (1H, m), 7,2 ppm (1H, m), 5,0 ppm (2H, d) 4,35 ppm (2H, q), 3,9 ppm (3H, s), 2,55 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,792 g (2,29 mmol) de la amida C (ver el esquema 1) se refluye con 1,37 g de hierro y 0,23 ml de 36% de HCl acuoso en una mezcla de etanol/agua para dar 0,312 g (46%) del producto D esperado (ver el esquema 1)

punto de fusión 120°C

MS (ES^+), m/z = 299

^{1}H NMR ($CDCl_3$, 400 MHz)

7,6-7,3 ppm (3H, m), 7,0 ppm (1H, m), 6,9 ppm (1H, s), 4,6 ppm (2H, q), 4,1 ppm (2H, d), 3,9 ppm (3H, s), 2,4 ppm (3H, s), 1,5 ppm (3H, t)

116

EJEMPLO 19

5-(2-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo R_2 = etilo, R_3 = 2-aminofenilo)

Paso 7

De acuerdo con M8, 1,11 g (5,56 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,5 g de clorhidrato de 2-amino-2'-nitroacetofenona para dar 0,246 g (44%) de una amida del tipo C (ver el esquema 1)

Rf (CH_2Cl_2/MeOH 90/10) = 0,87

^{1}H NMR ($CDCl_3$, 400 MHz)

9,3 ppm (1H, s), 8,2 ppm (1H, m), 7,8 ppm (1H, m), 7,6-7,5 ppm (2H, m), 4,6 ppm (2H, d) 4,1 ppm (2H, q), 2,5 ppm (3H, s), 1,4 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,237 g (0,66 mmol) de la amida C (ver el esquema 1) se refluye con 0,4 g de hierro y 0,07 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,08 g (43%) del producto D esperado (ver el esquema 1)

punto de fusión 156°C

MS (ES^+), m/z = 284

^{1}H NMR ($CDCl_3$, 400 MHz)

7,5 ppm (1H, m), 7,2 ppm (1H, m), 6,8-6,5 ppm (5H, m), 4,6 ppm (2H, q), 4,15 ppm (2H, d), 2,4 ppm (3H, s), 1,5 ppm (3H, t)

EJEMPLO 20

1-Etil-5-(2-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 2-metoxifenilo)

Paso 7

De acuerdo con M8, 0,24 g (1,22 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,245 g (1,22 mmol) de clorhidrato de 2-amino-2'-metoxiacetofenona (J Org Chem , 37, 2494-2496, 1972) para dar 0,197 g (47%) de una amida del tipo C (ver el esquema 1)

Rf (CH_2Cl_2/MeOH 95/5) = 0,8

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (1H, m), 7,9 ppm (1H, CONH), 7,55 ppm (1H, m), 7,05 ppm (2H, m), 4,95 ppm (2H, d), 4,35 ppm (2H, q), 4,0 ppm (3H, s), 2,55 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,19 g (0,55 mmol) de la amida C (ver el esquema 1) se refluye con 0,33 g de hierro y 0,055 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,07 g (43%) del producto D esperado (ver el esquema 1)

punto de fusión 214°C

MS (ES^+), m/z = 299

^1H NMR ($CDCl_3$, 400 MHz)

7,75 ppm (1H, m), 7,4 ppm (1H, m), 7,1 ppm (1H, m), 7,0 ppm (1H, m), 6,45 ppm (1H, s), 4,6 ppm (2H, q), 4,0 ppm (2H, d), 3,9 ppm (3H, s), 2,4 ppm (3H, s), 1,5 ppm (3H, t)

EJEMPLO 21

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = etilo, R_3 = fenilo)

Paso 3

De acuerdo con M1, 9 g (46 mmol) de etil 5-terc-butil-2H-pirazol-3-carboxilato y 11,61 g de $NaNO_3$ reaccionan en 90 ml de H_2SO_4 concentrado para dar 4,5 g (41%, polvo blanco) de un compuesto del tipo A4 (ver el esquema 1)

MDS (ES-), m/z = 240

Rf (CH_2Cl_2/acetona 90/10) = 0,54

Paso 5

De acuerdo con M5, 4,8 g (19,8 mmol) del compuesto A7 (ver el esquema 1) reaccionan con 1,74 ml (22 mmol) de yodometano para dar 4 g de un compuesto del tipo A5 (ver el Esquema 1) (aceite amarillo 75%)

119 175

MS (ES+), m/z = 270

^{1}H NMR ($CDCl_3$, 400 MHz)

1,35 ppm (12H, m), 1,4 ppm (3H, t), 4,35 ppm (4H, q)

Paso 6

4 g (14,8 mmol) del compuesto A5 (ver el esquema 1) reaccionan con 0,89 g (22 mmol) de hidróxido de sodio disuelto en una mezcla de etanol/agua para dar 3,2 g de un compuesto del tipo A (ver el esquema 1) (polvo blanco, 89%)

MS (ES-), m/z = 240

^{1}H NMR (DMSO, 400 MHz)

1,05 ppm (9H, s), 1,1 ppm (3H, t), 4,05 ppm (2H, q), 14,4 ppm (1H, m)

Paso 7

De acuerdo con M8, 1 g (4,1 mmol) del compuesto A (ver el esquema 1) reacciona con 0,7 g de clorhidrato de 2-amino-acetofenona para dar 1,3 g (88%) de un compuesto del tipo C (ver el esquema 1)

MS (ES+), m/z = 359

^{1}H NMR ($CDCl_3$, 400 MHz)

1,45 ppm (9H, s), 1,5 ppm (3H, t), 4,2 ppm (2H, q), 4,95 ppm (2H, d), 7,4 ppm (1H, m), 7,55 ppm (2H, m), 7,65 ppm (1H, t), 8,0 ppm (2H, d)

Paso 8

De acuerdo con M11, 1,3 g (3,6 mmol) del compuesto C (ver el esquema 1) se refluye con 0,5 ml de HCl y 2,16 g de hierro en una mezcla de etanol/agua para dar 0,2 g (18%) del producto D esperado (ver el esquema 1)

MS (ES^+), m/z = 311

punto de fusión 160°C

^1H NMR ($CDCl_3$, 400 MHz)

1,5 ppm (12H,t), 4,1 ppm (2H, d), 4,55 ppm (2H, q), 6,7 ppm (1H, m), 7,45 ppm (3H, m) 8,0 ppm (2H, d)

EJEMPLO 22

3-Metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = metilo R_2 = propilo, R_3 = fenilo)

Paso 9

0,57 g (2 mmol) de 3-metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona se refluye en tolueno con 1,6 g (4 mmol) del reactivo de Lawesson para dar 0,58 g (97%) de un compuesto del tipo E (ver el esquema 1)

MS (ES+), m/z = 299

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (3H, t), 1,95 ppm (2H, m), 2,4 ppm (3H, s), 4,2 ppm (2H, m), 4,75 ppm (2H, t), 7,4 ppm (3H, m), 7,95 ppm (2H, d), 8,65 ppm (1H, m)

punto de fusión 156°C

EJEMPLO 23

1-Etil-3-metil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diapezin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = p-tolilo)

Paso 7

De acuerdo con M8, 0,31 g (1,56 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 0,29 g (1,56 mmol) de clorhidrato de 2-amino-4'-metilacetofenona para dar 0,5 g (98%) de una amida del tipo C (ver el esquema 1)

Rf (CH_2Cl_2/MeOH 90/10) = 0,85

^{1}H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (3H, m), 7,3 ppm (2H, m) 4,95 ppm (2H, d) 4,35 ppm (2H, q), 2,55 ppm (3H, s), 2,45 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,5 g (1,51 mmol) de la amida C (ver el esquema 1) se refluye con 0,94 g de hierro y 0107 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,15 g (34%) del producto D esperado (ver el esquema 1)

punto de fusión 185°C

MS (ES^+), m/z = 283

^1H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (2H, d), 7,25 ppm (2H, d) 6,5 ppm (1H, s) 4,6 ppm (2H, q), 4,1 ppm (2H, d), 2,4 ppm (6H, s), 1,5 ppm (3H, t)

EJEMPLO 24

5-(3-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R = metilo, R_2 = etilo R_3 = 3-aminofenilo)

Paso 7

De acuerdo con M8, 0,92 g (4,62 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico reacciona con 1 g de clorhidrato de 2-amino-3'-nitroacetofenona para dar 1,3 g (78%) de una amida del tipo C (ver el esquema 1)

Rf (CH_2Cl_2/MeOH 90/10) = 0,89

^1H NMR ($CDCl_3$, 400 MHz)

9,1 ppm (1H, s), 8,8 ppm (1H, s), 8,4 ppm (1H, m), 8,5 ppm (1H, m), 7,8 ppm (1H, m), 4,95 ppm (2H, d), 4,3 ppm (2H, q), 2,5 ppm (3H, s), 1,5 ppm (3H, t)

Paso 8

De acuerdo con M11, 1,3 g (3,6 mmol) de la amida C (ver el esquema 1) se refluye con 2,15 g de hierro y 0,38 ml de 36% de

123 146

HCl en una mezcla de etanol/agua para dar 0,34 g (34%) del producto D esperado (ver el esquema 1)

punto de fusión 80°C

MS (ES^+), m/z = 284

^1H NMR ($CDCl_3$, 400 MHz)

7,35 ppm (1H, m), 7,2 ppm (2H, m), 6,8 ppm (2H, m), 4,6 ppm (2H, q), 4,05 ppm (2H, d), 3,8 ppm (2H, bs), 2,4 ppm (3H, s), 1,5 ppm (3H, t)

EJEMPLO 25

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = terc-butilo, R_2 = etilo, R_3 = fenilo)

Paso 9

0,37 g (2,2 mmol) de 3-terc-butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona reacciona con 0,96 g (4,4 mmol) del reactivo de Lawesson para dar 0,25 g de un polvo amarillo (66%)

MS (ES+), m/z = 327

punto de fusión = 230°C

^1H NMR ($CDCl_3$, 400 MHz)

1,45 ppm (9H, s), 1,5 ppm (3H, m), 4,2 ppm (2H, m), 4,8 ppm (2H, q), 7,45 ppm (3H, m), 8,0 ppm (2H, d), 8,55 ppm (1H, m)

EJEMPLO 26

5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = etilo, R_3 = 4-aminofenilo)

Paso 7

De acuerdo con M8, 1,2 g (4,9 mmol) de ácido 5-terc-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico reacciona con 1,06 g de clorhidrato de 2-amino-4'-nitroacetofenona para dar 1,15 g (58%) de una amida del tipo C (ver el esquema 1)

MS (ES-), m/z = 402

^{1}H NMR ($CDCl_3$, 400 MHz)

1,4 ppm (9H, s), 1,5 ppm (3H, t), 4,25 ppm (2H, q), 4,95 ppm (2H, d), 7,4 ppm (1H, m), 8,15 ppm (2H, d), 8,35 (2H, d)

Paso 8

De acuerdo con M11, 1,15 g (2,8 mmol) de la amida C (ver el esquema 1) se refluye con 0,5 ml de HCl y 1,7 g de hierro en una mezcla de etanol/agua para dar 0,43 g (48%) del producto D esperado (ver el esquema 1)

MS (ES+) m/z = 326

punto de fusión 189°C

^{1}H NMR ($CDCl_3$, 400 MHz)

1,45 ppm (12H, m), 3,95 ppm (2H, s), 4,05 ppm (2H, d), 4,5 ppm (2H, q), 6,2 ppm (1H, m), 6,65 ppm (2H, d), 7,8 ppm (2H, d)

MS (ES+), m/z = 285

punto de fusión = 250°C

EJEMPLO 29

5-(4-Aminofenil)-3-metil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = propilo, R_3 = 4-aminofenilo)

Paso 7

De acuerdo con M8, 1,5 g (7 mmol) de ácido 5-metil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 1,52 g (7 mmol) de clorhidrato de 2-amino-4'-nitro-acetofenona para dar 2,5 g (95%) de una amida del tipo C (ver el esquema 1)

Rf (5/5 de ciclohexano/acetato de etilo) = 0,5

^{1}H NMR ($CDCl_3$, 400 MHz)

8,4 ppm (2H, d), 8,2 ppm (2H, d), 8 ppm (1H, m), 5 ppm (2H, d), 4,25 ppm (2H, t) 2,55 ppm (3H, s), 1,9 ppm (2H, m), 0,95 ppm (3H, t)

Paso 8

De acuerdo con M11, 2,5 g (6,7 mmol) de la amida C (ver el esquema 1) se refluye con 4,1 g de hierro y 0,83 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,75 g (40%) del producto D esperado (ver el esquema 1)

punto de fusión 225°C

MS (ES+), m/z = 298

^{1}H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (1H, m), 7,8 ppm (2H, d) 6,7 ppm (2H, d), 4,9 ppm (2H, s), 4,45 ppm (2H, t), 4 ppm (2H, d), 2,35 ppm (3H, s), 1,85 ppm (2H, m), 0,9 ppm (3H, t)

EJEMPLO 30

3-Metil-5-fenil-1-(2,2,2-trifluoroetil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = 2,2,2-trifluoroetilo, R_3 = fenilo)

Paso 7

De acuerdo con M8, 0,8 g (3,2 mmol) de ácido 5-metil-4-nitro-(2,2,2-trifluoroetil)-2H-pirazol-3-carboxílico (A) reacciona con 1,54 g (3,2 mmol) de clorhidrato de 2-aminoacetofenona para dar 0,14 g (12%) de una amida del tipo C (ver el esquema 1)

Rf (5/5 de ciclohexano/acetato de etilo) = 0,76

MS (ES+), m/z = 371

^{1}H NMR ($CDCl_3$, 400 MHz)

8,5 ppm (1H, s), 8,0 ppm (2H, d), 7,7 ppm (1H, m), 7,55 ppm (2H, m), 5,2 ppm (2H, m), 5,0 ppm (2H, d), 2,6 ppm (3H, s)

Paso 8

De acuerdo con M11, 0,14 g (0,38 mmol) de la amida C (ver el esquema 1) se refluye con 0,23 g de hierro y 0,046 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,1 g (80,5%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 323

^{1}H NMR ($CDCl_3$, 400 MHz)

9,0 ppm (2H, m), 7,5 ppm (3H, m), 6,6 ppm (1H, t), 5,3 ppm (2H, m), 4,2 ppm (2H, d), 2,5 ppm (3H, s)

EJEMPLO 31

5-Ciclohexil-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = ciclohexilo)

Síntesis de la α-amino cetona

De acuerdo con M6, 2,7 g (13,2 mmol) de 2-bromo-1-ciclohexiletanona (Tetrahedron, 48, 1, 67-78, 1992) se mezclan con 1,92 g (13,7 mmol) de hexametilentetramina en 20 ml de cloroformo La mezcla se calienta a 48°C durante 4 horas y luego se evapora hasta secarse El residuo se recoge en 20 ml de etanol y 9 ml de 36% de ácido clorhídrico Después de dejarla toda al noche a temperatura ambiente, el medio de reacción se filtra El filtrado se evapora hasta secarse para dar un aceite que se cristaliza desde éter dietílico Después de la filtración y el secado se obtienen 2,08 g (80%) de

clorhidrato de 2-amino-1-ciclohexiletanona en la forma de un a pasta

MS (ES+), m/z = 141

Rf (80/20 de CH_2Cl_2/MeOH) 0,31

Paso 7

De acuerdo con M8, 1,8 g (8,9 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 1,6 g (8,9 mmol) de clorhidrato de 2-amino-1-ciclohexiletanona para dar 1,15 g (40%) de una amida del tipo C (ver el esquema 1)

Rf (5/5 de ciclohexano/acetato de etilo) = 0,48

^{1}H NMR ($CDCl_3$, 400 MHz)

7,6 ppm (1H, bs), 4,4 ppm (2H, d) 4,3 ppm (2H, q), 2,5 ppm (3H, s), 2,4 ppm (1H, m), 2,0 a 1,3 ppm (13H, m)

Paso 8

De acuerdo con M11, 0,65 g (2 mmol) de la amida C (ver el esquema 1) se refluye con 1,2 g de hierro y 0,2 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,35 g (64%) del producto D esperado (ver el esquema 1)

punto de fusión 50°C

MS (ES+), m/z = 275

^{1}H NMR ($CDCl_3$, 400 MHz)

6,6 ppm (1H, t), 4,6 ppm (2H, q), 3,6 ppm (2H, d), 2,5 ppm (1H, td), 2,4 ppm (3H, s), 1,9 a 1,3 ppm (10H, m), 1,5 ppm (3H, t)

EJEMPLO 32

1-Etil-3-metil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 4-piridilo)

Paso 7

De acuerdo con M8, 1,24 g (6,2 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 1,3 g (6,2 mmol) de clorhidrato de 2-amino-1-pirid-4-il-etanona (J Med Chem , 38, 17, 3342-3350, 1995, J Amer Chem Soc , 67, 1468-1472, 1945) para dar 0,77 g (39%) de una amida del tipo C (ver el esquema 1)

Rf (80/20 de CH_2Cl_2/acetona) = 0,39

^1H NMR ($CDCl_3$, 400 MHz)

9,4 ppm (1H, t) 8,7 ppm (2H, d), 7,8 ppm (1H, d), 4,8 ppm (2H, d), 4,1 ppm (2H, q) 2,3 ppm (3H, s), 1,2 ppm (3H, t)

Paso 8

De acuerdo con M11, 0,76 g (2,4 mmol) de la amida C (ver el esquema 1) se refluye con 0,43 g de hierro y 0,24 ml de 36% de

130

HCl en una mezcla de etanol/agua para dar 0,1 g (15%) del producto D esperado (ver el esquema 1)

punto de fusión 148°C

MS (ES+), m/z = 270

^{1}H NMR ($CDCl_3$, 400 MHz)

8,8 ppm (2H, d), 8,3 ppm (1H, t), 7,9 ppm (2H, d), 4,4 ppm (2H, q), 4,1 ppm (2H, d), 2,3 ppm (3H, s), 1,4 ppm (3H, t)

EJEMPLO 33

5-terc-Butil-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = terc-butilo)

Paso 7

De acuerdo con M8, 0,66 g (3,3 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,5 g (3,3 mmol) de clorhidrato de 2-amino-3,3-dimetil-butan-2-ona (J Org Chem , 53, 5, 1113-1114, 1988) para dar 0,72 g (73,5%) de una amida del tipo C (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/MeOH) = 0,88

^{1}H NMR ($CDCl_3$, 400 MHz)

7,6 ppm (1H, bs), 4,5 ppm (2H, d), 4,3 ppm (2H, q), 2,6 ppm (3H, s), 1,5 ppm (3H, t), 1,3 ppm (9H, s)

Paso 8

De acuerdo con M11, 0,71 g (2,4 mmol) de la amida C (ver el esquema 1) se refluye con 1,43 g de hierro y 0,24 ml de 36% de HCl en una mezcla de etanol/agua para dar 0,27 g (46%) del producto D esperado (ver el esquema 1)

punto de fusión 120°C

MS (ES+), m/z = 249

^{1}H NMR ($CDCl_3$, 400 MHz)

6,6 ppm (1H, t), 4,5 ppm (2H, q) 3,7 ppm (2H, d), 2,3 ppm (3H, s), 1,4 ppm (3H, t), 1,2 ppm (9H, s)

EJEMPLO 34

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = butilo, R_2 = etilo, R_3 = fenilo)

Paso 7

De acuerdo con M8, 1 g (4,1 mmol) de ácido 5-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,7 g (4,1 mmol) de clorhidrato de 2-aminoacetofenona para dar 1,25 g (86%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 359

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, d), 7,8 ppm (1H, bs), 7,7 ppm (1H, m), 7,5 ppm (2H, m), 5,0 ppm (2H, d), 4,3 ppm (2H, q), 3,0 ppm (2H, m), 1,7 ppm (2H, m) 1,5 ppm (5H, m) 1,0 (3H, t)

Paso 8

De acuerdo con M11, 1,25 g (3,5 mmol) de la amida C (ver el esquema 1) se refluye con 2,1 g de hierro y 0,5 ml de 36% de HCl en una mezcla de etanol/agua para dar el producto D esperado (ver el esquema 1)

punto de fusión 105,4°C

MS (ES+), m/z = 311

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, m), 7,5 ppm (3H, m), 4,6 ppm (2H, q), 4,1 ppm (2H, d), 2,8 ppm (2H, m), 1,9 ppm (7H, m), 1,0 ppm (3H, t)

EJEMPLO 35

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = etilo, R_3 = terc-butilo)

Paso 7

De acuerdo con M9, 0,4 g (1,76 mmol) de ácido 2-etil-5-isopropil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,266 g (1,76 mmol) de clorhidrato de 1-amino-3,3-dimetilbutan-2-ona (J Org Chem , 53, 5, 1113-1114, 1988) para dar 0,38 g (67%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 325

Paso 8

De acuerdo con M12, 0,38 g (1,17 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,32 g de dihidrato de cloruro de estaño para dar 0,32 g (68%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 277

^{1}H NMR (DMSO, 400 MHz)

8,2 ppm (1H, t), 4,4 ppm (2H, q), 3,6 ppm (2H, d) 3,1 ppm (1H, m), 1,3 ppm (3H, t), 1,25 ppm (6H, d), 1,2 ppm (9H, s)

EJEMPLO 36

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = etilo, R_3 = p-tolilo)

Paso 7

De acuerdo con M9, 0,4 g (1,76 mmol) de ácido 2-etil-5-isopropil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,327 g (1,76 mmol) de clorhidrato de 1-amino-1-p-toliletanona para dar 0,32 g (51%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 359

^{1}H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (2H, d), 7,7 ppm (1H, bs), 7,3 ppm (2H, d), 5,0 ppm (2H, d), 4,3 ppm (2H, q), 3,6 ppm (1H, m), 2,4 ppm (3H, s), 1,5 ppm (3H, t), 1,3 ppm (6H, d)

Paso 8

De acuerdo con M12, 0,32 g (1,17 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,01 g de dihidrato de cloruro de estaño para dar 0,13 g (47%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 311

^{1}H NMR (DMSO, 400 MHz)

8,2 ppm (1H, t), 7,9 ppm (2H, d), 7,3 ppm (2H, d), 4,4 ppm (2H, q), 4,0 ppm (2H, d), 3,2 ppm (1H, m), 2,3 ppm (3H, s) 1,3 ppm (3H, t), 1,2 ppm (6H, d)

EJEMPLO 37

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

(R_1 = isopropilo, R_2 = etilo, R_3 = 4-cianofenilo)

Paso 7

De acuerdo con M9, 0,4 g (1,76 mmol) de ácido 2-etil-5-isopropil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,346 g (1,76 mmol) de clorhidrato de 4-(2-aminoetanoil)benzonitrilo (Yakugaku Zasshi 72 305-307 1952)

para dar 0,27 g (41%) de una amida del tipo C (ver el esquema 1)

MS (ES-), m/z = 368

^{1}H NMR ($CDCl_3$, 400 MHz)

8,1 ppm (2H, d), 7,8 ppm (2H, d), 7,75 ppm (1H, bs) 5,0 ppm (2H, d), 4,3 ppm (2H, m), 3,5 ppm (1H, m), 1,5 ppm (3H, m), 1,3 ppm (6H, m)

Paso 8

De acuerdo con M12, 0,27 g (0,7 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 0,82 g de dihidrato de cloruro de estaño para dar 0,077 g (33%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 322

^{1}H NMR (DMSO, 400 MHz)

8,3 ppm (1H, t), 8,2 ppm (2H, m), 8,0 ppm (2H, m), 4,45 ppm (2H, q), 4,05 ppm (2H, m) 3,2 ppm (1H, m), 1,4 ppm (3H, t), 1,3 ppm (6H, d)

EJEMPLO 38

1-Etil-3-isopropil-5-(4-pirrolidin-1-il-fenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

R_1 = isopropilo, R_2 = etilo, R_4 = 4-(1-pirrolidil)fenilo

Síntesis de la α-amino cetona B con R_3 = 4-(1-pirrolidinil)fenilo

De acuerdo con M6, 16,1 g (60 mmol) de 2-bromo-1-(4-(1-pirrolidinil)fenil)etanona se mezclan con 8,75 g (62,4 mmol) de hexametilentetramina en 240 ml de cloroformo La mezcla se calienta a 48°C durante 4 horas y luego se filtra a temperatura ambiente El precipitado se recoge en 88 ml de etanol y 44 ml de 36% de ácido clorhídrico Después de agitar toda la noche a temperatura ambiente, el medio de reacción se filtra El filtrado se evapora hasta secarse para dar un aceite que se cristaliza desde etanol Después de la filtración, el lavado del precipitado con 20 ml de agua y el secado, se obtienen 6,3 g (43%) de clorhidrato de 2-amino-1-(4-(1-pirrolidin)fenil)-etanona en la forma de un polvo beige que contiene 3% en peso de NH_4Cl

^1H NMR (DMSO, 400 MHz)

8,1 ppm (3H, s), 7,65 ppm (2H, d) 6,45 ppm (2H, d), 4,2 ppm (2H, m), 3,2 ppm (4H, m), 1,8 ppm (4H, t)

Paso 7

De acuerdo con M9, 0,4 g (1,76 mmol) de ácido 2-etil-5-isopropil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,437 g (1,76 mmol) de clorhidrato de 2-amino-1-(4-(1-pirrolidin)fenil)-etanona (97%) para dar 0,36 g (49%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 414

Paso 8

De acuerdo con M12, 0,36 g (0,87 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 0,98 g (5 eq) de dihidrato de cloruro de estaño para dar 0,143 g (45%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 366

^{1}H NMR (DMSO, 400 MHz)

8,2 ppm (1H, t), 7,9 ppm (2H, d), 6,6 ppm (2H, d), 4,4 ppm (2H, q), 3,95 ppm (2H, d), 3,3 ppm (4H, m), 3,2 ppm (1H, m), 2 ppm (4H, m), 1,35 ppm (3H, t), 1,3 ppm (6H, d)

EJEMPLO 39

5-(2,4-Dimetoxifenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = etilo, R_3 = 2,4-dimetoxifenilo)

Paso 7

De acuerdo con M9, 0,4 g (1,76 mmol) de ácido 2-etil-5-isopropil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,408 g (1,76 mmol) de clorhidrato de 2-amino-1-(2,4-dimetoxifenil)-etanona para dar 0,47 g (66%) de una amida del tipo C (ver el esquema 1)

MS (ES+) m/z = 40

Paso 8

De acuerdo con M12, 0,47 g (1,16 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,31 g de dihidrato de cloruro de estaño para dar 0,152 g (37%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 357

^{1}H NMR (DMSO, 400 MHz)

8,3 ppm (1H, t), 7,6 ppm (1H, d), 6,7 ppm (2H, m), 4,45 ppm (2H, q), 3,9 ppm (3H, s), 3,85 ppm (2H, d), 3,8 ppm (3H, s), 3,2 ppm (1H, m) 1,4 ppm (3H, t), 1,2 ppm (6H, d)

EJEMPLO 40

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = propilo, R_3 = terc-butilo)

Paso 7

De acuerdo con M9, 0,425 g (1,76 mmol) de ácido 5-isopropil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,267 g (1,76 mmol) de clorhidrato de 1-amino-3,3-dimetilbutan-2-ona (J Org Chem , 53, 5, 1113-1114, 1988) para dar 0,43 g (72%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 33

Paso 8

De acuerdo con M12, 0,43 g (1,27 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,43 g de dihidrato de cloruro de estaño para dar 0,236 g (64%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 291

^{1}H NMR (DMSO, 400 MHz)

8,25 ppm (1H, bs), 4,4 ppm (2H, bs), 3,6 ppm (2H, s), 3,2 ppm (1H, m), 1,8 ppm (2H, m), 1,3 ppm (6H, d), 1,25 ppm (9H, s), 0,85 ppm (3H, t)

EJEMPLO 41

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = propilo, R_3 = p-tolilo)

Paso 7

De acuerdo con M9, 0,425 g (1,76 mmol) de ácido 5-isopropil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,327 g (1,76 mmol) de clorhidrato de 2-amino-1-p-toliletanona para dar 0,37 g (57%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 373

Paso 8

140 145

De acuerdo con M12, 0,37 g (1 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,12 g de dihidrato de cloruro de estaño para dar 0,176 g (55%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 325

^{1}H NMR (DMSO, 400 MHz)

8,1 ppm (1H, t), 7,7 ppm (1H, d), 7,1 ppm (2H, d) 4,25 ppm (2H, t), 3,8 ppm (2H, d), 3,1 ppm (1H, m), 2,2 ppm (3H, s), 1,6 ppm (2H, m), 1,1 ppm (6H, d), 0,7 ppm (3H, t)

EJEMPLO 42

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

(R_1 = isopropilo, R_2 = propilo R_3 = 4-cianofenilo)

Paso 7

De acuerdo con M9, 0,425 g (1,76 mmol) de ácido 5-isopropil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,346 g (1,76 mmol) de clorhidrato de 4-(2-aminoetanoil)benzonitrilo (Yakugaku Zasshi, 72, 305-307, 1952) para dar 0,32 g (48%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 384

^{1}H NMR ($CDCl_3$, 400 MHz)

8,1 ppm (2H, d), 7,85 ppm (2H, d), 7,7 ppm (1H, bs), 5,0 ppm (2H, d), 4,3 ppm (2H, m), 3,6 ppm (1H, m), 1,9 ppm (2H, m), 1,3 ppm (6H, d), 0,9 ppm (3H, m)

Paso 8

De acuerdo con M12, 0,32 g (0,834 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 0,94 g de cloruro de estaño para dar 0,076 g (27%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 336

^{1}H NMR (DMSO, 400 MHz)

8,3 ppm (1H, bs), 8,15 ppm (2H, m), 8,0 ppm (2H, m), 4,4 ppm (2H, q), 4,05 ppm (2H, m), 3,2 ppm (1H, m), 1,8 ppm (2H, m), 1,3 ppm (6H, d), 0,9 ppm (3H, t)

EJEMPLO 43

5-(4,2-Dimetoxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = propilo, R_3 = 2,4-dimetoxifenilo)

Paso 7

De acuerdo con M9, 0,425 g (1,76 mmol) de ácido 5-isopropil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,407 g (1,76 mmol) de clorhidrato de 2-amino-1-(2,4-dimetoxi-

fenil)etanona para dar 0,54 g (73%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 41

Paso 8

De acuerdo con M12, 0,54 g (1,29 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,46 g (5 eq) de dihidrato de cloruro de estaño para dar 0,246 g (51%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 371

^{1}H NMR (DMSO, 400 MHz)

8,3 ppm (1H, bs), 7,55 ppm (1H, m), 6,7 ppm (2H, m), 4,4 ppm (2H, t), 3,9 ppm (3H, s), 3,8 ppm (5H, m), 3,2 ppm (1H, m), 1,3 ppm (6H, m), 0,8 ppm (3H, m)

EJEMPLO 44

3,5-Di-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = etilo, R_3 = terc-butilo)

Paso 7

De acuerdo con M9, 0,425 g (1,76 mmol) de ácido 5-terc-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,267 g (1,76 mmol) de clorhidrato de 1-amino-3,3-

dimetilbutan-2-ona para dar 0,37 g (62%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 339

Paso 8

De acuerdo con M12, 0,37 g (1,09 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,23 g de dihidrato de cloruro de estaño para dar 0,17 g (54%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 291

^{1}H NMR (DMSO, 400 MHz)

8,2 ppm (1H, t), 4,4 ppm (2H, q), 3,5 ppm (2H, d), 1,35 ppm (9H, s), 1,3 ppm (3H, t), 1,2 ppm (9H, s)

EJEMPLO 45

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = etilo, R_3 = p-tolilo)

Paso 7

De acuerdo con M9, 0,425 g (1,76 mmol) de ácido 5-terc-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,327 g (1,76 mmol) de clorhidrato de 2-amino-1-p-tolil etanona para dar 0,39 g (60%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 373

Paso 8

De acuerdo con M12, 0,39 g (1,05 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,18 g de dihidrato de cloruro de estaño para dar 1,181 g (53%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 325

^{1}H NMR (DMSO, 400 MHz)

8,25 ppm (1H, t), 7,9 ppm (2H, d), 7,3 ppm (2H, d), 4,4 ppm (2H, q), 4,0 ppm (2H, d), 2,35 ppm (3H, s), 1,4 ppm (9H, s), 1,35 ppm (3H, t)

EJEMPLO 46

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

(R_1 = terc-butilo, R_2 = etilo, R_3 = 4-cianofenilo)

Paso 7

De acuerdo con M9, 0,425 g (1,76 mmol) de ácido 5-terc-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,346 g (1,76 mmol) de 4-(2-aminoetanoil)benzonitrilo (Yakugaku Zasshi, 72, 305-307, 1952) para dar 0,33 g (49%) de una amida del tipo C (ver el esquema 1)

MS (ES+) m/z = 384

^{1}H NMR ($CDCl_3$, 400 MHz)

8,1 ppm (2H, d), 7,8 ppm (2H, d), 5,0 ppm (2H, d), 4,3 ppm (2H, m), 1,5 a 1,4 ppm (12H, m)

Paso 8

De acuerdo con M12, 0,33 g (0,86 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 0,97 g de dihidrato de cloruro de estaño para dar 0,091 g (32%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 336

^{1}H NMR (DMSO, 400 MHz)

8,3 ppm (1H, t), 8,2 ppm (2H, d), 8,0 ppm (2H, d), 4,45 ppm (2H, m), 4,0 ppm (2H, d), 1,4 ppm (9H, s) 1,35 ppm (3H, t)

EJEMPLO 47

3-terc-Butil-5-(2,4-dimetoxifenil)-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = etilo, R_3 = 2,4-dimetoxifenilo)

Paso 7

De acuerdo con M9, 0,425 g (1,76 mmol) de ácido 5-terc-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,407 g (1,76 mmol) de clorhidrato de 2-amino-1-(2,4-dimetoxifenil)etanona (J Chem Res Miniprint, 7, 1581-1597, 1989)

para dar 0,56 g (76%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 419

Paso 8

De acuerdo con M12, 0,56 g (1,34 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,51 g de dihidrato de cloruro de estaño para dar 0,112 g (23%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 371

^{1}H NMR (DMSO, 400 MHz)

8,2 ppm (1H, t), 7,4 ppm (1H, d), 6,5 ppm (2H, m), 4,3 ppm (2H, m), 3,75 ppm (3H, s), 3,65 ppm (5H, bs) 1,2 ppm (9H, s), 1,15 ppm (3H, t)

EJEMPLO 48

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = propilo, R_3 = terc-butilo)

Paso 7

De acuerdo con M9, 0,449 g (1,76 mmol) de ácido 5-terc-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,267 g (1,76 mmol) de clorhidrato de 1-amino-3,3-dimetilbutan-2-ona (J Org Chem 53 5 1113-1114 1988)

para dar 0,42 g (68%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 353

Paso 8

De acuerdo con M12, 0,42 g (1,2 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,34 g de dihidrato de cloruro de estaño para dar 0,154 g (42%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 305

^{1}H NMR (DMSO, 400 MHz)

8,2 ppm (1H, t), 4,3 ppm (2H, t), 3,55 ppm (2H, d), 1,7 ppm (2H, m), 1,4 ppm (9H, s), 1,2 ppm (9H, s), 0,8 ppm (3H, t)

EJEMPLO 49

3-terc-Butil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = propilo, R_3 = p-tolilo)

Paso 7

De acuerdo con M9, 0,449 g (1,76 mmol) de ácido 5-terc-butil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,327 g (1,76 mmol) de clorhidrato de 2-amino-1-p-tolil etanona para dar 0,43 g (63%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 387

Paso 8

De acuerdo con M12, 0,43 g (1,11 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,26 g de dihidrato de cloruro de estaño para dar 0,163 g (43%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 339

^{1}H NMR (DMSO, 400 MHz)

8,3 ppm (1H, t), 7,9 ppm (2H, m), 7,3 ppm (2H, m), 4,4 ppm (2H, t) 4,0 ppm (2H, d), 2,4 ppm (3H, s), 1,8 ppm (2H, 7), 1,4 ppm (9H, s), 0,85 ppm (3H, t)

EJEMPLO 50

4-(3-terc-Butil-8-oxo-1-propil-1,6,7,8-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

(R_1 = terc-butilo, R_2 = propilo, R_3 = 4-cianofenilo)

Paso 7

De acuerdo con M9, 0,449 g (1,76 mmol) de ácido 5-terc-butil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,346 g (1,76 mmol) de clorhidrato de 4-(2-aminoetanoil)benzonitrilo (Ykagaku Zasshi, 72, 305-307, 1952) para dar 0,36 g (51%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 396

Paso 8

De acuerdo con M12, 0,36 g (0,9 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,02 g de dihidrato de cloruro de estaño para dar 0,116 g (37%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 350

^{1}H NMR (DMSO, 400 MHz)

8,35 ppm (1H, t), 8,2 ppm (2H, m), 8,0 ppm (2H, m), 4,4 ppm (2H, t), 4,0 ppm (2H, d), 1,8 ppm (2H, m), 1,4 ppm (9H, s) 0,85 ppm (3H, t)

EJEMPLO 51

3-terc-Butil-5-(2,4-dimetoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = propilo, R_3 = 2,4-dimetoxifenilo)

Paso 7

De acuerdo con M9, 0,449 g (1,76 mmol) de ácido 5-terc-butil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,407 g (1,76 mmol) de clorhidrato de 2-amino-1-(2,4-dimetoxifenil)etanona (J Chem Res Miniprint, 7, 1581-1597, 1989) para dar 0,59 g (77%) de una amida del tipo C (ver el esquema 1)

MS (ES+), m/z = 433

Paso 8

De acuerdo con M12, 0,59 g (1,36 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,54 g de dihidrato de cloruro de estaño para dar 0,184 g (35%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 385

^{1}H NMR (DMSO, 400 MHz)

8,4 ppm (1H, t), 7,55 ppm (1H, m), 6,6 ppm (2H, m), 4,35 ppm (2H, q), 3,9 ppm (3H, s), 3,8 ppm (5H, m), 1,8 ppm (2H, m), 1,35 ppm (9H, s), 0,8 (3H, t)

EJEMPLO 52

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = butilo R_2 = etilo R_3 = fenilo)

Paso 9

0,65 g (2 mmol) de 3-butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona reacciona con 1,77 g (4 mmol) de reactivo de Lawesson y se refluye en tolueno toda la noche para dar 0,4 g (60%) de la tiolactama de tipo E deseada (ver el Esquema 1)

Rf (95/5 de CH_2Cl_2/acetona) = 0,65

punto de fusión 151,5°C

MS (ES+), m/z = 327

^1H NMR ($CDCl_3$, 400 MHz)

8,8 ppm (1H, t) 8,0 ppm (2H, m), 7,4 ppm (3H, m), 4,8 ppm (2H, q), 4,2 ppm (2H, d), 2,8 ppm (2H, m), 1,7 ppm (2H, m) 1,5 ppm (3H, m), 1,4 ppm (2H, m), 0,9 ppm (3H, t)

EJEMPLO 53

1-Etil-3-metil-5-pirid-3-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 3-piridilo)

Paso 7

De acuerdo con M8, 1,9 g (9,5 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 2 g (9,5 mmol) de clorhidrato de 2-amino-1-pirid-3-iletanona (Chem Pharm Bull , 32, 7, 2536-2553, 1984, J Amer Chem Soc , 67, 1468-1472, 1945) para dar 2,2 g (73%) de una amida del tipo C (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,27

^1H NMR ($CDCl_3$, 400 MHz)

9,55 ppm (1H, t), 9,2 ppm (1H, s), 8,8 ppm (1H, d), 7,95 ppm (2H, m), 5,0 ppm (2H, d), 4,2 ppm (2H, q), 2,4 ppm (3H, s), 1,4 ppm (3H, t)

152 1

Paso 8

De acuerdo con M12, 1,1 g (3,47 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,9 g (5 eq) de dihidrato de cloruro de estaño para dar 0,26 g (28%) del producto D esperado (ver el esquema 1)

punto de fusión 178°C

MS (ES+), m/z = 270

^{1}H NMR (DMSO, 400 MHz)

9,2 ppm (1H, bs), 8,7 ppm (1H, d), 8,4 ppm (1H, d), 8,3 ppm (1H, t), 7,5 ppm (1H, dd), 4,4 ppm (2H, q), 4,1 ppm (2H, d), 2,3 ppm (3H, s), 1,4 ppm (3H, t)

EJEMPLO 54

1-Etil-3-metil-5-pirid-2-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 2-piridilo)

Paso 7

De acuerdo con M8, 1,9 g (9,5 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 2 g (9,5 mmol) de clorhidrato de 2-amino-1-pirid-2-iletanona (J Amer Chem Soc , 67, 1468-1472, 1945 J Chem Soc , 753, 1938) para dar 2,2 g (73%) de una amida del tipo C (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,38

MMS (ES+), m/z = 318

^{1}H NMR ($CDCl_3$, 400 MHz)

9,5 ppm (1H, bs), 8,8 ppm (1H, m), 8,0 ppm (2H, m), 7,7 ppm (1H, m), 5,0 ppm (2H, d), 4,2 ppm (2H, q), 2,4 ppm (3H, s), 1,4 ppm (3H, t)

Paso 8

De acuerdo con M12, 1,1 g (3,47 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,9 g (5 eq) de dihidrato de cloruro de estaño para dar 0,19 g (20%) del producto D esperado (ver el esquema 1)

punto de fusión 153°C

MS (ES+), m/z = 270

^{1}H NMR (DMSO, 400 MHz)

8,7 ppm (1H, d), 8,3 ppm (21H, m), 8,0 ppm (1H, t), 7,5 ppm (1H, dd), 4,5 ppm (2H, q), 4,4 ppm (2H, d), 2,3 ppm (3H, s), 1,4 ppm (3H, t)

EJEMPLO 55

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

(R_1 = metilo, R_2 = etilo, R_3 = fenilo)

Paso 10

De acuerdo con M13, 2 g (7 mmol) de 1-etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona reaccionan con 0,21 g de 80% de hidruro de sodio en THF en reflujo durante 1 hora, luego se agrega 0,52 ml de yoduro de metilo, a temperatura ambiente La mezcla se refluye durante 2 horas para dar 2,1 g (10%) del metilsulfanilo G esperado (ver el esquema 1)

MS (ES+), m/z = 299

^{1}HH NMR ($CDCl_3$, 400 MHz)

8,1 ppm (2H d), 7,5 ppm (3H, m), 4,5 ppm (4H, m), 2,5 ppm (3H, s), 2,4 ppm (3H, s), 1,5 ppm (3H, t)

Paso 11

0,5 g (1,67 mmol) del metilsulfanilo G reacciona con 0,14 g (2 eq) de cianamida para dar 0,29 g (60%) del producto F deseado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/MeOH) = 0,32

punto de fusión = 280°C

MS (ES+), mm/z = 293

^{1}H NMR (DMSO, 400 MHz)

9,5 ppm (1H, s), 8,2 ppm (2H, m), 7,5 ppm (3H, m), 4,5 ppm (2H, q), 4,2 ppm (2H, s), 2,3 ppm (3H, s), 1,4 ppm (3H, t)

EJEMPLO 56

159 160

N-[4-(1-Etil-3-metil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)fenil]-(fenilsulfonil)bencensulfonamida (R_1 = metilo, R_2 = etilo, R_3 = 4-N-(fenilsulfonil)bencensulfonamidofenilo)

0,2 g (0,7 mmol) de 5-(4-aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona, se introduce en un matraz de base circular y se agregan 10 ml de acetonitrilo, luego 0,158 g (1,41 mmol) de 1,4-diazabiciclo[2 2 2]octano, y 0,116 ml (0,91 mmol) de cloruro de bencensulfonilo La mezcla de la reacción se agita toda la noche a temperatura ambiente y luego se evapora hasta secarse para dar 0,54 g de un compuesto aceitoso El producto crudo se purifica mediante cromatografía rápida usando el siguiente gradiente de elución desde CH_2Cl_2 hasta 98/2 de CH_2Cl_2/metanol Después de la evaporación y la cristalización desde metanol, se obtienen 0,19 g (48%) de un polvo amarillo

MS (ES+), m/z = 564

punto de fusión = >230°C

^{1}H NMR ($CDCl_3$, 400 MHz)

1,5 ppm (3H, t), 2,4 ppm (3H, s) 4,1 ppm (2H, m), 4,55 ppm (2H, q), 6,25 ppm (1H, m), 7,1 ppm (2H, m), 7,6 ppm (4H, m), 7,7 ppm (2H, m), 7,85 ppm (6H, m)

156

EJEMPLO 57

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-iliden-cianamida

(R_1 = terc-butilo, R_2 = etilo, R_3 = fenilo)

Paso 10

De acuerdo con M13, 1,65 g (5,05 mmol) de 3-terc-butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona reaccionan con 0,15 g de 80% de hidruro de sodio en THF en reflujo durante 1 hora, luego se agrega 0,38 ml de yoduro de metilo, a temperatura ambiente La mezcla se refluye durante 2 horas para dar 1,55 g (90%) del metilsulfanilo G esperado (ver el esquema 1)

Paso 11

0,5 g (1,47 mmol) del metilsulfanilo G reacciona con 0,12 g (2 eq) de cianamida para dar 0,185 g (38%) del producto de tipo F esperado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/metanol) = 0,57

punto de fusión = 250°C

MS (ES+), mm/z = 335

^{1}H NMR (DMSO, 400 MHz)

9,5 ppm (1H, s), 8,1 ppm (2H, d), 7,5 ppm (3H, d), 4,5 ppm (2H, q), 4,2 ppm (2H, bs), 1,4 ppm (6H, s), 1,35 ppm (3H, m)

EJEMPLO 58

1-Ciclopropilmetil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = ciclopropilmetilo, R_3 = fenilo)

Paso 5,

De acuerdo con M5, 1,9 g (9,5 mmol) de etil-3-metil-4-nitro-1H-5-pirazolcarboxilato (comercial), reaccionan con 5 g (37 mmol) de (bromometil)ciclopropano (comercial) en la presencia de 1,43 g (9,5 mmol) de yoduro de sodio para dar 1,14 g (48%) de un pirazol A5 (ver el esquema 1)

Rf (80/20 de ciclohexano/EtOAc) = 0,47

^{1}H NMR ($CDCl_3$, 400 MHz)

4,45 ppm (2H, q), 4,05 ppm (2H, d), 2,5 ppm (3H, s) 1,4 ppm (3H, t), 1,3 ppm (1H, m), 0,6 ppm (2H, m), 0,4 ppm (2H, m)

Paso 6

1,14 g (4,5 mmol) del pirazol A5 (ver el esquema 1) reacciona con 0,27 g (6,75 mmol) de hidróxido de sodio en una mezcla de metanol y agua para dar 0,93 g (91%) de un pirazol del tipo A (ver el esquema 1)

MS (ES-), m/z = 224

Paso 7

158 163

De acuerdo con M9, 0,5 g (2,22 mmol) de ácido 2-(ciclopropilmetil)-5-metil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,38 g (2,22 mmol) de clorhidrato de 2-aminoacetofenona para dar 1 g del compuesto C (ver el esquema 1)

MS (ES+), m/z = 343

Paso 8

De acuerdo con M12, 1 g (2,9 mmol) del compuesto C (ver el esquema 1) se refluye en etanol con 2,5 g (11 mmol) de dihidrato de cloruro de estaño para dar 0,17 g (27%) del producto D esperado (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,42

MS (ES+), m/z = 295

^1H NMR ($CDCl_3$, 400 MHz)

7,95 ppm (1H, m), 7,5 ppm (3H, m), 6,15 ppm (1H, t), 4,4 ppm (2H, d), 4,1 ppm (2H, d), 2,45 ppm (3H, s), 1,45 ppm (1H, m), 0,5 ppm (2H, m), 0,45 ppm (2H, m)

EJEMPLO 59

1-Alil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = alilo, R_3 = fenilo)

139

Paso 5,

De acuerdo con M5, 2,5 g (12,5 mmol) de etil-3-metil-4-nitro-1H-5-pirazolcarboxilato (comercial), reaccionan con 1,09 ml (12,5 mmol) de bromuro de alilo (comercial) en la presencia de 0,38 g (12,5 mmol) de 80% de hidruro de sodio en 1,2-dimetoxietano para dar 0,35 g (12%) de un pirazol A5 (ver el esquema 1)

Rf (70/30 de ciclohexano/EtOAc) = 0,53

^{1}H NMR ($CDCl_3$, 400 MHz)

5,9-6,0 ppm (1H, m), 5,3 ppm (1H, d), 5,2 ppm (1H, d), 4,8 ppm (2H, d), 4,45 ppm (2H, q) 2,5 ppm (3H, s), 1,4 ppm (3H, t)

Paso 6

0,35 g (1,46 mmol) del pirazol A5 (ver el esquema 1) reacciona con 0,09 g (2,25 mmol) de hidróxido de sodio en una mezcla de metanol y agua para dar 0,071 g (23%) de un pirazol del tipo A (ver el esquema 1)

MS (ES-), m/z = 210

Paso 7

De acuerdo con M9, 0,071 g (0,34 mmol) de ácido 2-alil-5-metil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,058 g (0,34 mmol) de clorhidrato de 2-aminoacetofenona para dar 0,174 g del compuesto C (ver el esquema 1)

160 165.

Paso 8

De acuerdo con M12, 0,174 g (0,5 mmol) del compuesto C (ver el esquema 1) se refluye en etanol con 0,385 g (1,68 mmol) de dihidrato de cloruro de estaño para dar 0,01 g (11%) del producto D esperado (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,30

MS (ES+), m/z = 281

EJEMPLO 60

1-Etil-3-metil-5-(4-triflurometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 4-triflurometilfenilo)

Paso 7

De acuerdo con M9, 0,33 g (1,67 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,4 g (1,67 mmol) de clorhidrato de 2-amino-1-(4-trifluorometil-fenil)etanona (J Amer Chem Soc , 75, 5884-5886, 1953, J Org Chem , 42, 5, 868-871, 197) para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 383

Paso 8

De acuerdo con M12, 0,64 g (1,67 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,9 g (5 eq.) de dihidrato

161 177

de cloruro de estaño para dar 0,153 g (27%) del producto de tipo D esperado (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,22

punto de fusión = 195°C

MS (ES+), m/z = 337

^1H NMR (DMSO, 400 MHz)

8,4 ppm (1H, t), 8,3 ppm (2H, d), 8,0 ppm (2H, d), 4,5 ppm (2H, q), 4,1 ppm (2H, d), 2,4 ppm (3H, s) 1,4 ppm (3H, t)

EJEMPLO 61

1-Etil-3-isopropil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = etilo, R_3 = 4-trifluorometilfenilo)

Paso 7

De acuerdo con M9, 0,38 g (1,67 mmol) de ácido 2-etil-5-isopropil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,4 g (1,67 mmol) de clorhidrato de 2-amino-1-(4-trifluorometilfenil)etanona (J Amer Chem Soc , 75, 5884-5886, 1953, J Org Chem , 42, 5, 868-871, 197) para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 411

Paso 8

De acuerdo con M12, 0,69 g (1,67 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,9 g (5 eq) de dihidrato de cloruro de estaño para dar 0,161 g (26,5%) del producto de tipo D esperado (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,28

punto de fusión = 133°C

MS (ES+), m/z = 364

^1H NMR (DMSO, 400 MHz)

8,3 ppm (1H, t), 8,2 ppm (2H, d), 7,9 ppm (2H, d), 4,4 ppm (2H, q), 4,0 ppm (2H, d), 3,3 ppm (1H, m), 1,4 a 1,3 ppm (9H, m)

EJEMPLO 62

1-Etil-3-metil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = etilo R_3 = 4-trifluorometilfenilo)

Paso 7

De acuerdo con M9, 0,4 g (1,67 mmol) de ácido 5-terc-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,4 g (1,67 mmol) de clorhidrato de 2-amino-1-(4-trifluorometil-fenil)etanona (J Amer Chem Soc , 75, 5884-5886, 1953, J Org Chem , 42, 5, 868-871, 197) para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+) m/z = 425

Paso 8

De acuerdo con M12, 0,712 g (1,67 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 1,9 g (5 eq) de dihidrato de cloruro de estaño para dar 0,14 g (22%) del producto de tipo D esperado (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,33

punto de fusión = 144°C

MS (ES+), m/z = 379

^{1}H NMR (DMSO, 400 MHz)

8,3 ppm (1H, t), 8,2 ppm (2H, d), 7,9 ppm (2H, d) 4,4 ppm (2H, q), 4,1 ppm (2H, d), 1,4 ppm (9H, s), 1,35 ppm (3H, t)

EJEMPLO 63

1-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = isopropilo, R_2 = propilo, R_3 = p-tolilo)

Paso 9

0,9 g (2,7 mmol) de 3-isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona reacciona con 2,24 g (5,53 mmol) de reactivo de Lawesson y se refluye en tolueno toda la noche para dar 0,73 g (77%) de la tiolactama de tipo E (ver el esquema 1)

Rf (CH_2Cl_2) = 0,22

punto de fusión = 162,9°C

164 1 169

MS (ES+), m/z = 340,9

^{1}H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (3H, t), 1,35 ppm (6H, m), 1,9 ppm (2H, m), 2,4 ppm (3H, s), 3,3 ppm (1H, m), 4,15 ppm (2H, m), 4,75 ppm (2H, m), 7,2 ppm (2H, d), 7,9 ppm (2H, d), 8,65 ppm (1H, m)

EJEMPLO 64

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = terc-butilo, R_2 = propilo, R_3 = terc-butilo)

Paso 9

1,5 g (4,9 mmol) de 3,5-di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona reacciona con 4 g (9,8 mmol) de reactivo de Lawesson y se refluye en tolueno toda la noche para dar 1,4 g (90%) de la tiolactama de tipo E (ver el esquema 1)

Rf (80/20 ciclohexano/EtOAc) = 0,54

punto de fusión = 205°C

MS (ES+), m/z = 321

^{1}H NMR ($CDCl_3$, 400 MHz)

9,0 ppm (1H, m), 4,7 ppm (2H, m), 1,9 ppm (2H, m), 1,4 ppm (9H, s), 1,25 ppm (9H, s), 0,9 ppm (3H, t)

165

EJEMPLO 65

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = isopropilo, R_2 = propilo, R_3 = terc-butilo)

Paso 9

0,35 g (4,9 mmol) de 5-terc-butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona reacciona con 0,98 g (2,4 mmol) de reactivo de Lawesson y se refluye en tolueno toda la noche para dar 0,25 g (68%) de la tiolactama de tipo E (ver el esquema 1)

Rf (80/20 ciclohexano/EtOAc) = 0,67

punto de fusión = 165°C

MS (ES+), m/z = 307

^{1}H NMR ($CDCl_3$, 400 MHz)

8,8 ppm (1H, m), 4,7 ppm (2H, m), 3,75 ppm (2H, m), 3,2 ppm (1H, m), 1,9 ppm (2H, m), 1,3 ppm (6H, d), 1,25 ppm (9H, s), 0,9 ppm (3H, t)

EJEMPLO 66

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = isopropil, R_2 = etilo, R_3 = p-tolilo)

Paso 9

0,62 g (2 mmol) de 1-etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona reacciona con 1,62 g (4 mmol) de reactivo de Lawesson y se refluye en tolueno toda la noche para dar 0,567 g (87%) de la tiolactama de tipo E (ver el esquema 1)

Rf (98/2 CH_2Cl_2/MeOH) = 0,46

punto de fusión =178°C

MS (ES+), m/z = 327

^1H NMR ($CDCl_3$, 400 MHz)

8,5 ppm (1H, bs), 7,8 ppm (2H, d), 7,15 ppm (2H, d), 4,75 ppm (2H, q), 4,1 ppm (2H, bs), 3,2 ppm (1H, m), 2,3 ppm (3H, s), 1,4 ppm (3H, t), 1,3 ppm (6H, d)

EJEMPLO 67

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = isopropilo, R_2 = etilo, R_3 = terc-butilo)

Paso 9

0,4 g (1,45 mmol) de 5-terc-butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona reacciona con 1,17 g (2,9 mmol) de reactivo de Lawesson y se refluye en tolueno toda la noche para dar 0,193 g (46%) de la tiolactama de tipo E (ver el esquema 1)

Rf (98/2 CH_2Cl_2/MeOH) = 0,43

punto de fusión = 218°C

MS (ES+), m/z = 293

^1H NMR ($CDCl_3$, 400 MHz)

10,35 ppm (1H, bs), 4,65 ppm (2H, q), 3,9-3,3 ppm (2H, bs), 3,1 ppm (1H, m), 1,3 ppm (3H, t), 1,2 ppm (6H, d), 1,15 ppm (9H, s)

EJEMPLO 68

(±)3-sec-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = sec-butilo, R_2 = etilo, R_3 = fenilo)

Síntesis del pirazol (después de los pasos 1, 2, 3, 5 y 6)

Paso 1

3,44 g (149,8 mmol) de sodio se disuelven en porciones en 200 ml de etanol anhidro bajo nitrógeno, a temperatura ambiente Se agregan 20,35 ml (149,8 mmol) de oxalato de dietilo en 60 ml de etanol anhidro Se agregan 15 g (149,8 mmol) de 3-metil-2-pentanona La mezcla de la reacción se refluye durante 3 horas, bajo nitrógeno y con agitación y luego se evapora hasta secarse, el residuo se recoge en 300 ml de HCl (1,2 N) y luego se extrae con éter dietílico (3 veces 200 ml) La fase orgánica se seca sobre sulfato de sodio y luego se concentra para dar 26,1 g (89%) de un aceite incoloro (compuesto A1, ver

Rf (60/40 de CH_2Cl_2/heptano) = 0,4

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (3H, t), 1,1 ppm (3H, d), 1,4 ppm (3H, t), 1,5 ppm (1H, m), 1,7 ppm (1H, m), 2,4 ppm (2H, m), 4,3 ppm (2H, q), 6,4 ppm (1H, s), 14,6 ppm (1H, m)

Paso 2

8,25 g (125 mmol) de hidróxido de potasio se disuelven en 120 ml de agua y el medio de reacción se enfría a 0°C Se agregan 25 g (125 mmol) del compuesto A1 (ver el esquema 1) en porciones y la mezcla se agita durante 15 minutos a 0°C Se agregan 16,3 g (130,11 mmol) de sulfato de hidrazina y la mezcla luego se agita durante 20 minutos a 0°C Se agita a temperatura ambiente durante toda la noche, después de lo cual se agregan 200 ml de agua y la mezcla se extrae con diclorometano (3 x 200 ml) La fase orgánica obtenida se lava con una solución de NaCl saturado (1 x 200 ml) y luego se seca sobre sulfato de sodio y se concentra Se obtienen 24,5 g de un polvo

El producto se purifica mediante cromatografía rápida (95/5 de CH_2Cl_2/acetona) para dar 17,6 g (68%) de un polvo blanco (compuesto A6, ver el esquema 1)

Rf (95/5 de CH_2Cl_2/acetona) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

0,85 ppm (3H, t), 1,3 ppm (3H, d), 1,35 ppm (3H, t), 1,6 ppm (1H, m), 2,8 ppm (1H, m), 4,4 ppm (2H, m), 6,6 ppm (1H, s) 11,6 ppm (1H, m)

Paso 3

De acuerdo con M3, 20,7 g (89,5 mmol) de nitrato de cobre(II) hemipentahidratado (2,5 H_2O) y 100 ml de anhídrido trifluoroacético se introducen en un matraz de base circular, la mezcla se agita bajo nitrógeno durante 5 minutos y se agregan 17 g del compuesto A6 (ver el esquema 1) (80,87 mmol) disueltos en 100 ml de cloroformo Esta mezcla se refluye con agitación y bajo nitrógeno durante 5 horas Este producto se purifica mediante cromatografía rápida (98/2 de CH_2Cl_2/acetona) para dar 20 g de un aceite azulado Este producto se recoge en 200 ml de HCl (10%) y luego se extrae con éter dietílico (3 veces 300 ml) y la fase orgánica se seca y se concentra para dar 16,81 g (70%) de un aceite incoloro (compuesto A7, ver el esquema 1)

MS (ES-), m/z = 239,91

Rf (97/3 de CH_2Cl_2/acetona) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (3H, t), 1,4 ppm (6H, m), 1,7 ppm (2H, m), 3,4 ppm (1H, m) 4,4 ppm (2H, q), 11,6 ppm (1H, m)

Paso 5

170 13

De acuerdo con M4, 0,92 g (3,81 mmol) del compuesto A7 (ver el esquema 1) y 0,5 ml (3,81 mmol) de sulfato de dietilo se introducen en un matraz de base circular y la mezcla se refluye luego con agitación y bajo nitrógeno durante 1 hora 30 minutos Después de enfriar a temperatura ambiente, se agregan 6 g de hielo y 15 ml de HCl (10%) y la mezcla se agita y luego se extrae con diclorometano (3 veces 40 ml) La fase orgánica se seca y se concentra para dar 1,1 g de un aceite incoloro Este produto se purifica mediante cromatografía rápida (gradiente 9/1 a 7/3 de ciclohexano/acetato de etilo) para dar 0,8 g (78%) de un polvo blanco (compuesto A5, ver el esquema 1)

Rf (80/20 de ciclohexano/acetato de etilo) = 0,3

^{1}H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (3H, t), 1,35 ppm (3H, m), 1,45 ppm (6H, m), 1,6 ppm (1H, m), 1,8 ppm (1H, m) 3,3 ppm (1H, m), 4,25 ppm (2H, q), 4,5 ppm (2H, q)

Paso 6

8,3 g (33,80 mmol) del compuesto A5 (ver el esquema 1) se disuelven en 40 ml de metanol, luego se agrega una solución de 2 g (50,7 mmol) de hidróxido de sodio en 40 ml de agua La mezcla se agita a temperatura ambiente durante 2 horas Después de evaporar el metanol, el residuo se recoge en CH_2Cl_2, se agrega un volumen idéntico de agua luego se agrega ácido

clorhídrico concentrado (36%) a pH ácido, con agitación La fase orgánica se seca sobre Na_2SO_4 y se concentra para dar 7,5 g (98%) de un polvo blanco (compuesto A, ver el esquema 1)

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (3H, m), 1,3 ppm (3H, m), 1,5 ppm (3H, m), 1,6 ppm (1H, m), 1,8 ppm (1H, m), 3,3 ppm (1H, m), 4,5 ppm (2H, q), 9,3 ppm (1H, m)

Paso 7

De acuerdo con M9, 0,434 g (1,8 mmol) de ácido 5-sec-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,309 g (1,8 mmol) de clorhidrato de 2-aminoacetofenona para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 359

Paso 8

De acuerdo con M12, 0,65 g (1,8 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,25 g (5 eq) de dihidrato de cloruro de estaño para dar 0,14 g (25%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 311

^1H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (2H, m), 7,4 ppm (3H, m), 7,2 ppm (1H, m), 4,5 ppm (2H, q), 4,1 ppm (2H, t), 3,1 ppm (1H, m), 1,8 ppm (1H, m),

1,7 ppm (1H, m), 1,4 ppm (3H, t), 1,3 ppm (3H, d), 0,8 ppm (3H, t)

EJEMPLO 69

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-diyhidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = sec-butilo, R_2 = etilo, R_3 = 4-piridilo)

Síntesis del pirazol ver los pasos 1, 2, 3, 5 y 6 del Ejemplo 68

Paso 7

De acuerdo con M9, 0,434 g (1,8 mmol) de ácido 5-sec-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,376 g (1,8 mmol) de clorhidrato de 2-amino-1-pirid-4-iletanona (J Med Chem , 38, 17, 3342-3350, 1995, J Amer Chem Soc , 67, 1468-1472, 1945) para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 359,8

Paso 8

De acuerdo con M12, 0,65 g (1,8 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,25 g (5 eq) de dihidrato de cloruro de estaño para dar 0,135 g (24%) del roducto D esperado (ver el esquema 1)

p.pto de fusión 86°C-88,5°C

MS (ES+), m/z = 312

^{1}H NMR ($CDCl_3$, 400 MHz)

8,8 ppm (2H, d), 7,8 ppm (2H, d), 7,2 ppm (1H, m), 4,6 ppm (2H, q), 4,1 ppm (2H, d), 3,1 ppm (1H, m), 1,9 ppm (1H, m), 1,7 ppm (1H, m), 1,5 ppm (3H, t), 1,4 ppm (3H, d), 0,9 ppm (3H, q)

EJEMPLO 70

(±)3-sec-Butil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = sec-butilo, R_2 = propilo, R_3 = fenilo)

Síntesis del pirazol ver los pasos 1, 2, y 3 del ejemplo 68 y los siguientes pasos 5 y 6

Paso 5

De acuerdo con M5, 4,90 g (66,32 mmol) de Li_2CO_3 se agregan, bajo una corriente de nitrógeno, a una solución de 6,4 g (26,53 mmol) del compuesto A7 (ver el esquema 1) en 110 ml de DMF anhidro, luego se agregan 6,5 ml (66,32 mmol) de yodopropano El medio de reacción se calienta a 60°C durante 24 horas Se enfría a temperatura ambiente y luego se vierte en 100 ml de HCl (1,2 N), la exotermicidad se controla con un baño de hielo Después de extraer con diclorometano (3 veces 100 ml), la fase orgánica obtenida se lava con solución de NaCl sat rada (100 ml) se seca sobre Na_2SO_4 se evapora hasta

secarse para dar 7 g de un compuesto aceitoso El produto se purifica mediante cromatografía rápida (gradiente 70/30 a 60/40 de heptano/CH_2Cl_2) para dar 5 g (66%) de un aceite incoloro que se cristaliza (compuesto A5, ver el esquema 1)

Rf (50/50 de heptano/CH_2Cl_2) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

0,90 ppm (6H, m), 1,25 ppm (3H, m), 1,40 ppm (3H, m), 1,60 ppm (1H, m), 1,80 ppm (3H, m), 3,30 ppm (1H, m), 4,25 ppm (2H, q) 4,40 ppm (2H, q)

Paso 6

4,94 g (18,41 mmol) del compuesto A5 (ver el esquema 1) se disuelven en 21 ml de metanol, luego se agrega una solución de 1,1 g (27,61 mmol) de hidróxido de sodio en 21 ml de agua Esta mezcla se agita a temperatura ambiente durante 2 horas Después de evaporar el metanol, el residuo se recoge en CH_2Cl_2, se agrega un volumen idéntico de agua, luego se agrega ácido clorhídrico concentrado (36%) a pH ácido, con agitación La fase orgánica se seca sobre Na_2SO_4 y se concentra para dar 4,5 g (96%) de un polvo blanco (compuesto A, ver el esquema 1)

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (6H, m), 1,3 ppm (3H, d), 1,6 ppm (1H, m) 1,8 ppm (1H, m), 1,9 ppm (2H, m) 3,3 ppm (1H, m), 4,4 ppm (2H, q), 7,6 ppm (1H, m)

Paso 7

De acuerdo con M9, 0,46 g (1,8 mmol) de ácido 5-sec-butil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,31 g (1,8 mmol) de clorhidrato de 2-aminoacetofenona para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 373

Paso 8

De acuerdo con M12, 0,67 g (1,8 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,35 g (5 eq) de dihidrato de cloruro de estaño para dar 0,035 g (6%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 325

^{1}H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (2H, m), 7,5 ppm (3H, m), 6,7 ppm (1H, m), 4,5 ppm (2H, m), 4,1 ppm (2H, m), 3,1 ppm (1H, m), 2,0 ppm a 1,6 ppm (4H, m), 1,4 ppm (3H, d), 0,9 ppm (6H, m)

EJEMPLO 71

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = sec-butilo, R_2 = propilo, R_3 = 4-piridilo)

Síntesis del pirazol ver los pasos 1, 2, 3, 5, 6 del Ejemplo 70

Paso 7

De acuerdo con M9, 0,46 g (1,8 mmol) de ácido 5-sec-butil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,376 g (1,8 mmol) de clorhidrato de 2-amino-1-pirid-4-iletanona (J Med Chem , 38, 17, 3342-3350, 1995, J Amer Chem Soc , 67, 1468-1472, 1945) para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 373,6

Paso 8

De acuerdo con M12, 0,62 g (1,66 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,36 g (5 eq) de dihidrato de cloruro de estaño para dar 0,1 g (17,3%) del producto D esperado (ver el esquema 1)

punto de fusión, 110°C

MS (ES+), m/z = 325,8

^{1}H NMR ($CDCl_3$, 400 MHz)

8,7 ppm (2H, d), 7,7 ppm (2H, d), 7,0 ppm (1H, t), 4,5 ppm (2H, q), 4,0 ppm (2H, d), 3,1 ppm (1H, m), 1,9 ppm (2H, m), 1,8 ppm (1H, m), 1,7 ppm (1H, m), 1,3 ppm (3H, d), 0,9 ppm (3H, m), 0,8 ppm (3H, m)

EJEMPLO 72

3-Ciclohexil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo-[4,3-e][1,4]diazepin-8-ona

(R_1 = ciclohexilo, R_2 = etilo, R_3 = fenilo)

Síntesis del pirazol ver los siguientes pasos 1,2, 3, 5 y 6

Paso 1

2,46 g (107 mmol) de sodio se disuelven en porciones en 250 ml de etanol anhidro bajo nitrógeno, a temperatura ambiente Se agregan 14,52 ml (107 mmol) de oxalato de dietilo en 60 ml de etanol anhidro Se agregan 15 g (107 mmol) de acetilciclohexano La mezcla de la reacción se refluye durante 3 horas, bajo nitrógeno y con agitación y luego se evapora hasta secarse, el residuo se recoge en 300 ml de HCl (1,2 N) y luego se extrae con éter dietílico (3 veces 200 ml) La fase orgánica se seca sobre sulfato de sodio y luego se concentra para dar 23,2 g (96%) de un aceite incoloro (compuesto A1, ver el esquema 1)

Rf (60/40 de CH_2Cl_2/n-heptano) = 0,1

^1H NMR ($CDCl_3$, 400 MHz)

1,3 ppm (8H, m), 1,8 ppm (5H, m), 2,35 ppm (1H, m), 4,3 ppm (2H, q), 6,4 ppm (1H, s), 14,6 ppm (1H, m)

Paso 2

7 g (104 mmol) de hidróxido de potasio se disuelven en 110 ml de agua y el medio de reacción se enfría a 0°C Se agregan 25 g (110 mmol) del compuesto A1 (ver el esquema 1) en porciones y la mezcla se agita durante 15 minutos a 0°C Se agregan 13 5

g (104 mmol) de sulfato de hidrazina y la mezcla luego se agita durante 20 minutos a 0°C Se agita a temperatura ambiente durante toda la noche, después de lo cual se agregan 200 ml de agua y la mezcla se extrae con diclorometano (3 x 200 ml) La fase orgánica obtenida se lava con una solución de NaCl saturado (1 x 200 ml) y luego se seca sobre sulfato de sodio y se concentra Se obtienen 23,4 g de un polvo

El producto se purifica mediante cromatografía rápida (gradiente 97/3 a 90/10 de CH_2Cl_2/acetona) para dar 15 g (61%) de un polvo blanco (compuesto A6, ver el esquema 1)

Rf (95/5 de CH_2Cl_2/acetona) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

1,35 ppm (8H, m), 1,7 ppm (3H, m), 1,95 ppm (2H, m), 2,7 ppm (1H, m) 4,3 ppm (2H, q), 6,6 ppm (1H, s), 11,8 ppm (1H, m)

Paso 3

De acuerdo con M3, 12,77 g (54,93 mmol) de nitrato de cobre(II) hemipentahidratado (2,5 H_2O) y 100 ml de anhídrido trifluoroacético se introducen en un matraz de base circular, la mezcla se agita bajo nitrógeno durante 5 minutos y se agregan 11,1 g del compuesto A6 (ver el esquema 1) (49,93 mmol) disueltos en 100 ml de cloroformo Esta mezcla se refluye con agitación y bajo nitrógeno durante 5 horas Después de la evaporación hasta secarse, se obtienen 18,6 g de un aceite azulado Este producto se recoge en 200 ml de HCl

(10%) y luego se extrae con éter dietílico (3 veces 300 ml) y la fase orgánica se seca y se concentra para dar 16,1 g de un aceite incoloro Este producto se purfifica mediante cromatografía rápida (98/2 de CH_2Cl_2/acetona para dar 7,1 g (53%) de un polvo blanco (compuesto A7, ver el esquema 1)

Rf (97/3 de CH_2Cl_2/acetona) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

1,40 ppm (8H, m), 1,8 ppm (3H, m), 2,0 ppm (2H, m), 3,3 ppm (1H, m), 4,4 ppm (2H, q), 8,85 ppm (1H, m)

Paso 5

De acuerdo con M4, 1,02 g (3,81 mmol) del compuesto A7 (ver el esquema 1) y 0,5 ml (3,81 mmol) de sulfato de dietilo se introducen en un matraz de base circular y la mezcla se refluye luego con agitación y bajo nitrógeno durante 1 hora 30 minutos Después de enfriar a temperatura ambiente, se agregan 6 g de hielo y 15 ml de HCl (10%) y la mezcla se agita y luego se extrae con diclorometano (3 veces 40 ml) La fase orgánica se seca y se concentra para dar 1,1 g de un aceite incoloro Este produto se purifica mediante cromatografía rápida (5/5 de CH_2Cl_2/heptano) para dar 0,53 g (53%) de un polvo blanco (compuesto A5, ver el esquema 1)

Rf (9/1 de ciclohexano/acetato de etilo) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

1,4 ppm (11H, m), 1,8 ppm (3H, m), 1,95 ppm (2H, m) 3,1 ppm (1H, m), 4,25 ppm (2H, q), 4,5 ppm (2H, q)

Paso 6

5,07 g (17,16 mmol) del compuesto A5 (ver el esquema 1) se disuelven en 20 ml de metanol, luego se agrega una solución de 1,03 g (25,75 mmol) de hidróxido de sodio en 20 ml de agua Esta mezcla se agita a temperatura ambiente durante 2 horas Después de evaporar el metanol, el residuo se recoge en CH_2Cl_2, se agrega un volumen idéntico de agua, luego se agrega ácido clorhídrico concentrado (36%) a pH ácido, con agitación La fase orgánica se seca sobre Na_2SO_4 y se concentra para dar 4,6 g (100%) de un polvo blanco (compuesto A, ver el esquema 1)

^1H NMR ($CDCl_3$, 400 MHz)

1,1 ppm a 1,5 ppm (8H, m) 3,0 ppm (1H, m), 4,5 ppm (2H, q), 8,4 ppm (1H, m)

Paso 7

De acuerdo con M9, 0,48 g (1,8 mmol) de ácido 5-ciclohexil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,31 g (1,8 mmol) de clorhidrato de 2-aminoacetofenona para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 384,9

Paso 8

De acuerdo con M12, 0,69 g (1,8 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,46 g (5 eq) de dihidrato de cloruro de estaño para dar 0,103 g (17%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 337

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, m), 7,4 ppm (3H, m), 7,1 ppm (1H, m), 4,5 ppm (2H, q), 4,1 ppm (2H, d), 3,0 ppm (1H, m), 2,0 ppm (2H, m), 1,8 ppm (2H, m), 1,7 ppm (2H, m), 1,5 ppm a 1,2 ppm (7H, m)

EJEMPLO 73

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = ciclohexilo, R_2 = etilo, R_3 = 4-piridilo)

Síntesis del pirazol ver los pasos 1, 2, 3, 5 y 6 del ejemplo 72

Paso 7

De acuerdo con M9, 0,48 g (1,8 mmol) de ácido 5-ciclohexiletil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,376 g (1,8 mmol) de clorhidrato de 2-amino-1-pirid-4-iletanona (J Med Chem , 38, 17, 3342-3350, 1995 J Amer Chem Soc , 67, 1468-1472, 1945) para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+) m/z = 385 9

181

188

Paso 8

De acuerdo con M12, 0,63 g (1,63 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,12 g (5 eq) de dihidrato de cloruro de estaño para dar 0,092 g (15%) del producto D esperado (ver el esquema 1)

punto de fusión, 126°C-127°C

MS (ES+), m/z = 338

^{1}H NMR ($CDCl_3$, 400 MHz)

8,6 ppm (2H, d), 7,7 ppm (2H, d), 7,4 ppm (1H, t), 4,5 ppm (2H, q), 4,0 ppm (2H, d), 2,9 ppm (1H, m), 1,9 ppm (2H, m), 1,8 ppm (2H, m), 1,6 ppm (2H, m), 1,4 ppm (3H, m), 1,3 ppm (4H, m)

EJEMPLO 74

3-Ciclohexil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = ciclohexilo, R_2 = propilo, R_3 = fenilo)

Síntesis del pirazol ver los pasos 1, 2, y 3 del ejemplo 72 y los siguientes pasos 5 y 6

Paso 5

De acuerdo con M5, 2,07 g (28,06 mmol) de Li_2CO_3 se agregan, bajo una corriente de nitrógeno, a una solución de 3 g (11,22 mmol) del compuesto A7 (ver el esquema 1) en 60 ml de DMF anhidro, luego se agregan 2,73 ml (28,06 mmol) de yodopropano

El medio de reacción se calienta a 60°C durante 48 horas Después de enfriar a temperatura ambiente, la mezcla se vierte en 100 ml de HCl (1,2 N) y la exotermicidad se controla con un baño de hielo La mezcla se extrae con diclorometano (3 veces 100 ml) y la fase orgánica obtenida se lava con solución de NaCl saturado (100 ml), se seca sobre Na_2SO_4 y se concentra para dar 3,6 g de un compuesto aceitoso Este produto se purifica mediante cromatografía rápida (gradiente 70/30 a 30/70 de heptano/CH_2Cl_2) para dar 2,85 g (82%) de un aceite incoloro que se cristaliza (compuesto A5, ver el esquema 1)

Rf (60/40 de heptano/CH_2Cl_2) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (3H, t), 1,45 ppm (6H, m), 1,5 ppm (2H, m), 2,85 ppm (7H, m), 3,1 ppm (1H, q) 4,1 ppm (2H, q) 4,4 ppm (2H, q)

Paso 6

2,85 g (9,21 mmol) del compuesto A5 (ver el esquema 1) se disuelven en 10 ml de metanol, luego se agrega una solución de 0,55 g (13,81 mmol) de hidróxido de sodio en 10 ml de agua La mezcla se agita a temperatura ambiente durante 2 horas Después de evaporar el metanol, el residuo se recoge en CH_2Cl_2, se agrega un volumen idéntico de agua, luego se agrega ácido clorhídrico concentrado (36%) a pH ácido, con agitación La fase orgánica se seca sobre Na_2SO_4 y se concentra para dar 2,52 g (97%) de un polvo blanco (compuesto A, ver el esquema 1)

189

184

^{1}H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (3H, m), 1,2 ppm a 1,6 ppm (5H, m), 1,7 ppm a 2,0 ppm (7H, m), 3,1 ppm (1H, m), 4,4 ppm (2H, q), 8,7 ppm (1H, m)

Paso 7

De acuerdo con M9, 0,5 g (1,8 mmol) de ácido 5-ciclohexil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,31 g (1,8 mmol) de clorhidrato de 2-aminoacetofenona para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 399

Paso 8

De acuerdo con M12, 0,72 g (1,8 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,59 g (5 eq) de dihidrato de cloruro de estaño para dar 0,172 g (27%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 351

^{1}H NMR ($CDCl_3$, 400 MHz)

7,8 ppm (2H, m), 7,4 ppm (4H, m), 4,5 ppm (2H, q), 4,0 ppm (2H, d), 2,9 ppm (1H, m), 1,9 ppm a 1,7 ppm (10H, m), 1,3 ppm (2H, m), 0,9 ppm (3H, t)

EJEMPLO 75

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = ciclohexilo, R_2 = propilo, R_3 = 4-piridilo)

Síntesis del pirazol ver los pasos 1,2, 3, 5 y 6 del Ejemplo 74

Paso 7

De acuerdo con M9, 0,5 g (1,8 mmol) de ácido 5-ciclohexil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,376 g (1,8 mmol) de clorhidrato de 2-amino-1-pirid-4-iletanona (J Med Chem , 38, 17, 3342-3350, 1995, J Amer Chem Soc , 67, 1468-1472, 1945) para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 400

Paso 8

De acuerdo con M12, 0,65 g (1,63 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,24 g (5 eq) de dihidrato de cloruro de estaño para dar 0,055 g (8,6%) del producto D esperado (ver el esquema 1)

punto de fusión 152°C-153°C

MS (ES+), m/z = 352

^{1}H NMR ($CDCl_3$, 400 MHz)

8,7 ppm (2H, d), 7,7 ppm (2H, d), 6,9 ppm (1H, t), 4,4 ppm (2H, m), 4,5 ppm (2H, d), 2,9 ppm (1H, m), 1,9 ppm a 1,6 ppm (10H, m), 1,3 ppm (2H, m), 0,8 ppm (3H, t)

EJEMPLO 76

3-Ciclohexilmetil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = ciclohexilmetilo, R_2 = etilo R_3 = 4-piridilo)

Síntesis del pirazol ver los siguientes pasos 1, 2, 5, 3 y 6

Paso 1

4,33 g (188,26 mmol) de sodio se disuelven en porciones en 200 ml de etanol anhidro bajo nitrógeno, a temperatura ambiente Se agregan 25,6 ml (188,26 mmol) de oxalato de dietilo en 50 ml de etanol anhidro Se agregan 24 g (171,11 mmol) de acetonilciclohexano La mezcla de la reacción se refluye durante 3 horas, bajo nitrógeno y con agitación y luego se evapora hasta secarse, el residuo se recoge en 300 ml de HCl (1,2 N) y luego se extrae con éter dietílico (3 veces 200 ml) La fase orgánica se seca sobre sulfato de sodio y luego se concentra para dar 42,6 g (92%) de un aceite incoloro (compuesto A1, ver el esquema 1)

Rf (99/1 de CH_2Cl_2/n-heptano) = 0,5

^{1}H NMR ($CDCl_3$, 400 MHz)

1,0 ppm (2H, m), 1,25 ppm (3H, m), 1,4 ppm (3H, m), 1,7 ppm (6H, m), 1,8 ppm (1H, m), 2,35 ppm (2H, d), 4,4 ppm (2H, q), 6,3 ppm (1H, s) 14,6 ppm (1H, m)

Paso 2

12,9 g (195,4 mmol) de hidróxido de potasio se disuelven en 250 ml de agua y el medio de reacción se enfría a 0°C Se agregan 42,6 g (177 mmol) del compuesto A1 (ver el esquema 1) en porciones y la mezcla se agita durante 30 minutos a 0°C Se agregan 25,37 g (195 mmol) de sulfato de hidrazina y la mezcla luego se agita durante 20 minutos a 0°C Se agita a temperatura ambiente durante toda la noche, después de lo cual se agregan 200 ml de agua y la mezcla se extrae con diclorometano (3 x 200 ml) La fase orgánica obtenida se lava con una solución de NaCl saturado (1 x 200 ml) y luego se seca sobre sulfato de sodio y se concentra Se obtienen 40 g de un polvo

El producto se purifica mediante cromatografía rápida (99/1 a 95/5 de CH_2Cl_2/acetona) para dar 20,7 g (50%) de un polvo blanco (compuesto 6, ver el esquema 1)

Rf (97/3 de CH_2Cl_2/acetona) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (8H, m) 1,2 ppm (4H, m) 1,4 ppm (3H, m), 1,65 ppm (6H, m), 2,6 ppm (H, d), 6,6 ppm (1H, s), 10,5 ppm (1H, m)

Paso 5

De acuerdo con M4, 8,5 g (36 mmol) del compuesto A6 (ver el esquema 1) y 2,38 ml (18 mmol) de sulfato de dietilo se introducen en un matraz de base circular y la mezcla se calienta luego a 125°C-130°C con agitación y bajo nitrógeno

durante 4 horas Después de enfriar a temperatura ambiente, se agregan 120 g de hielo y 120 ml de HCl (1,2 N) con agitación y la mezcla resultante se extrae con diclorometano (3 veces 250 ml) La fase orgánica se seca y se concentra para dar 10,81 g de un aceite marrón Este produto se purifica mediante cromatografía rápida (9/1 de ciclohexano/acetato de etilo) para dar 5,76 g (60%) de un polvo blanco (compuesto A8, ver el esquema 1)

Rf (80/20 de ciclohexano/acetato de etilo) = 0,3

^{1}H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (2H, m), 1,2 ppm (4H, m), 1,4 ppm (5H, m), 1,60 ppm (6H, m), 2,5 ppm (2H, d), 4,35 ppm (2H, q), 4,5 ppm (2H, q), 6,6 ppm (1H, s)

Paso 3

De acuerdo con M3, 20,7 g (89,95 mmol) de nitrato de cobre(II) hemipentahidratado (2,5 H_2O) y 100 ml de anhídrido trifluoroacético se introducen en un matraz de base circular, la mezcla se agita bajo nitrógeno durante 5 minutos y se agregan 17 g del compuesto A8 (80,87 mmol) disueltos en 100 ml de cloroformo Esta mezcla se refluye con agitación y bajo nitrógeno durante 5 horas Este producto se purifica mediante cromatografía rápida (98/2 de CH_2Cl_2/acetona) para dar 20 g de un aceite azulado Este producto se recoge en 200 ml de HCl (1,2 N) y luego se extrae con éter dietílico (3 veces 300 ml)

y la fase orgánica se seca y se concentra para dar 16,81 g (70%) de un aceite incoloro (compuesto A5, ver el esquema 1)

MS (ES+), m/z = 309,90

Rf (70/30 de heptano/CH_2Cl_2) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

1,0 ppm (2H, m), 1,2 ppm (3H, m), 1,4 ppm (3H, m), 1,45 ppm (3H, m), 1,7 ppm (6H, m), 2,8 ppm (2H, d) 4,3 ppm (2H, q), 4,5 ppm (2H, q)

Paso 6

8,3 g (33,80 mmol) del compuesto A5 (ver el esquema 1) se disuelven en 40 ml de metanol, luego se agrega una solución de 2 g (50,7 mmol) de hidróxido de sodio en 40 ml de agua Esta mezcla se agita a temperatura ambiente durante 2 horas Después de evaporar el metanol, el residuo se recoge en CH_2Cl_2, se agrega un volumen idéntico de agua, luego se agrega ácido clorhídrico concentrado (36%) a pH ácido, con agitación La fase orgánica se seca sobre Na_2SO_4 y se concentra para dar 7,5 g (98%) de un polvo blanco (compuesto A, ver el esquema 1)

^1H NMR ($CDCl_3$, 400 MHz)

1,0 ppm (2H, m), 1,2 ppm (3H, m), 1,5 ppm (3H, t), 1,7 ppm (6H, m), 2,8 ppm (2H, d), 4,6 ppm (2H, q), 8,55 ppm (1H, m)

Paso 7

De acuerdo con M9, 0,281 g (1,8 mmol) de ácido 5-ciclohexilmetil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,376 g (1,8 mmol) de clorhidrato de 2-amino-1-pirid-4-iletanona (J Med Chem , 38, 17, 3342-3350, 1995, J Amer Chem Soc , 67, 1468-1472, 1945) para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 400,01

Paso 8

De acuerdo con M12, 0,61 g (1,53 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,02g (5 eq) de dihidrato de cloruro de estaño para dar 0,073 g (12%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 352,32

^{1}H NMR ($CDCl_3$, 400 MHz)

8,7 ppm (2H, d), 7,8 ppm (3H, d), 7,3 ppm (1H, t), 4,6 ppm (2H, q), 4,1 ppm (2H, d), 2,7 ppm (2H, d), 1,7 ppm (6H, m), 1,5 ppm (3H, t), 1,3 ppm a 1,0 ppm (5H, m)

EJEMPLO 77

3-Ciclohexilmetil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = ciclohexilmetilo, R_2 = propilo, R_3 = fenilo)

Síntesis del pirazolo ver los pasos 1 y 2 del ejemplo 76 y los siguientes pasos 5 3 y 6

Paso 5

De acuerdo con M5, 3,9 g (52,89 mmol) de Li_2CO_3 se agregan, bajo una corriente de nitrógeno, a una solución de 5 g (21,16 mmol) del compuesto A6 (ver el esquema 1) en 100 ml de DMF anhidro, luego se agregan 5,2 ml (52,89 mmol) de yodopropano El medio de reacción se calienta a 70°C durante 48 horas Después de enfriar a temperatura ambiente, la mezcla se vierte en 100 ml de HCl (1,2 N) y la exotermicidad se controla con un baño de hielo La mezcla se extrae con diclorometano (3 veces 200 ml) y la fase orgánica obtenida se lava con solución de NaCl saturado (200 ml), se seca sobre Na_2SO_4 y se concentra para dar 5,8 g de un aceite marrón Este produto se purifica mediante cromatografía rápida (gradiente 50/50 a 30/70 de heptano/CH_2Cl_2) para dar 1,15 g (20%) de un aceite incoloro que se cristaliza (compuesto A8, ver el esquema 1)

Rf (60/40 de heptano/CH_2Cl_2) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (5H, m), 1,2 ppm (3H, m), 1,4 ppm (3H, m) 1,7 ppm (6H, m), 1,8 ppm (2H, m), 2,5 ppm (2H, d) 4,3 ppm (2H, q) 4,5 ppm (2H, q), 6,6 ppm (1H, s)

Paso 3

De acuerdo cn M3, 0,96 g (4,13 mmol) de nitrato de cobre(II) hemipentahidratado (2,5 H_2O) y 20 ml de anhídrido trifluoroacético se introducen en un matraz de base circular y

la mezcla se agita bajo nitrógeno durante 5 minutos, luego se agregan 1,15 g del compuesto A8 (ver el esquema 1) (4,13 mmol) disueltos en 20 ml de cloroformo Esta mezcla se refluye, con agitación y bajo nitrógeno, durante 3 horas Este producto se recoge en 10 g de hielo y 40 ml de HCl (10%) y luego se extrae con diclorometano (3 veces 100 ml) y la fase orgánica se seca y se concentra para dar 1,3 g de un aceite incoloro El producto se purifica mediante cromatografía rápida (gradiente 70/30 a 50/50 de heptano/CH_2Cl_2) para dar 1,08 g (80%) de un polvo blanco (compuesto A5, ver el esquema 1)

Rf (60/40 de heptano/CH_2Cl_2) = 0,3

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (3H, m), 1,0 ppm a 1,3 ppm (5H, m), 1,4 ppm (3H, m), 1,7 ppm (6H, m), 1,9 ppm (2H, m) 2,7 ppm (2H, d), 4,1 ppm (2H, t), 4,5 ppm (2H, q)

Paso 6

1 g (3,09 mmol) del compuesto A5 (ver el esquema 1) se disuelven en 5 ml de metanol, luego se agrega una solución de 0,185 g (4,64 mmol) de hidróxido de sodio en 5 ml de agua La mezcla se agita a temperatura ambiente durante 2 horas Después de evaporar el metanol, el residuo se recoge en CH_2Cl_2, se agrega un volumen idéntico de agua, luego se agrega ácido clorhídrico concentrado (36%) a pH ácido, con agitación La

fase orgánica se seca sobre Na_2SO_4 y se concentra para dar 0,89 g (97%) de un polvo blanco (compuesto A, ver el esquema 1)

^1H NMR ($CDCl_3$, 400 MHz)

0,9 ppm a 1,0 ppm (5H, m), 1,2 ppm (3H, m) 1,4 ppm (3H, m), 1,6 ppm (6H, m), 1,9 ppm (2H, m), 2,7 ppm (2H, d), 4,1 ppm (2H, t), 4,5 ppm (2H, q)

Paso 7

De acuerdo con M9, 0,463 g (1,57 mmol) de ácido 5-ciclohexilmetil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,269 g (1,57 mmol) de clorhidrato de 2-aminoacetofenona para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 413,04

Paso 8

De acuerdo con M12, 0,65 g (1,57 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,24 g (5 eq) de dihidrato de cloruro de estaño para dar 0,092 g (14%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 364,90

^1H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, m), 7,5 ppm (3H, m), 6,4 ppm (1H, s), 4,5 ppm (2H, d), 2,7 ppm (2H, d), 1,9 ppm (2H, m), 1,7 ppm (6H, m), 1,3 ppm a 0,8 ppm (8H, m)

194

EJMPLO 78

3-Ciclohexilmetil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = ciclohexilmetilo, R = propilo, R_3 = 4-piridilo)

Síntesis del pirazol ver los pasos 1, 2, 5, 3 y 6 del ejemplo 77

Paso 7

De acuerdo con M9, 0,464 g (1,57 mmol) de ácido 5-ciclohexilmetil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 0,328 g (1,57 mmol) de clorhidrato de 2-amino-1-pirid-4-iletanona (J Med Chem , 38, 17, 3342-3350, 1995, J Amer Chem Soc , 67, 1468-1472, 1945) para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 414,02

Paso 8

De acuerdo con M12, 0,59 g (1,43 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 2,92 g (5 eq) de dihidrato de cloruro de estaño para dar 0,101 g (15,4%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 366,38

^{1}H NMR ($CDCl_3$, 400 MHz)

8,7 ppm (2H, d) 7,7 ppm (2H, d) 6,9 ppm (1H, m), 4,5 ppm (2H, m), 4,0 ppm (2H, d), 2,7 ppm (2H, d), 1,8 ppm (3H, m), 1,7 ppm (5H, m), 1,0 ppm a 0,8 ppm (8H, m)

EJEMPLO 79

3-Ciclohexilmetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = ciclohexilmetilo, R_2 = etilo, R_3 = fenilo)

Síntesis del pirazol ver los pasos 1, 2, 5, 3 y 6 del ejemplo 76

Paso 5

De acuerdo con M4, 8,5 g (36 mmol) del compuesto A6 (ver el esquema 1) y 2,38 ml (18 mmol) de sulfato de dietilo se introducen en un matraz de base circular y la mezcla se calienta luego a 125°C-130°C, con agitación y bajo nitrógeno durante 4 horas Después de enfriar a temperatura ambiente, se agregan 120 g de hielo y 120 ml de HCl (1,2 N) con agitación y la mezcla resultante se extrae con diclorometano (3 veces 250 ml) La fase orgánica se seca y se concentra para dar 10,81 g de un aceite marrón Este produto se purifica mediante cromatografía rápida (9/1 de ciclohexano/acetato de etilo) para dar 5,76 g (60%) de un polvo blanco (compuesto A8, ver el esquema 1)

Rf (80/20 de ciclohexano/acetato de etilo) = 0,3

^{1}H NMR ($CDCl_3$, 400 MHz)

0,9 ppm (2H, m), 1,2 ppm (4H, m), 1,4 ppm (5H, m), 1,6 ppm (6H, m) 2,5 ppm (2H, d), 4,35 ppm (2H, q), 4,5 ppm (2H, q), 6,6 ppm (1H, s)

Paso 3

De acuerdo con M3, 20,7 g (89,95 mmol) de nitrato de cobre(II) hemipentahidratado (2,5 H_2O) y 100 ml de anhídrido trifluoroacético se introducen en un matraz de base circular, la mezcla se agita bajo nitrógeno durante 5 minutos y se agregan 17 g del compuesto A8 (ver el esquema 1) (80,87 mmol) disueltos en 100 ml de cloroformo Esta mezcla se refluye con agitación y bajo nitrógeno durante 5 horas Este producto se purifica mediante cromatografía rápida (98/2 de CH_2Cl_2/acetona) para dar 20 g de un aceite azulado Este producto se recoge en 200 ml de HCl (10%) y luego se extrae con éter dietílico (3 veces 300 ml) y la fase orgánica se seca y se concentra para dar 16,81 g (70%) de un aceite incoloro (compuesto A5, ver el esquema 1)

MS (ES+), m/z = 309,90

Rf (70/30 de heptano/CH_2Cl_2) = 0,3

^{1}H NMR ($CDCl_3$, 400 MHz)

1,0 ppm (2H, m), 1,2 ppm (3H, m), 1,4 ppm (3H, m), 1,45 ppm (3H, m), 1,7 ppm (6H, m), 2,8 ppm (2H, d), 4,3 ppm (2H, q) 4,5 ppm (2H, q)

Paso 6

8,3 g (33,80 mmol) del compuesto A5 (ver el esquema 1) se disuelven en 40 ml de metanol, luego se agrega una solución de 2 g (50,7 mmol) de hidróxido de sodio en 40 ml de agua Esta mezcla se agita a temperatura ambiente durante 2 horas Después de evaporar el metanol, el residuo se recoge en CH_2Cl_2, se agrega un volumen idéntico de agua, luego se agrega ácido clorhídrico concentrado (36%) a pH ácido, con agitación La fase orgánica se seca sobre Na_2SO_4 y se concentra para dar 7,5 g (98%) de un polvo blanco (compuesto A, ver el esquema 1)

^1H NMR ($CDCl_3$, 400 MHz)

1,0 ppm (2H, m) 1,2 ppm (3H, m) 1,5 ppm (3H, t), 1,7 ppm (6H, m), 2,8 ppm (2H, d), 4,6 ppm (2H, q) 8,55 ppm (1H, m)

Paso 7

De acuerdo con M9, 0,281 g (1,8 mmol) de ácido 5-ciclohexilmetil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 0,309 g (1,8 mmol) de clorhidrato de 2-aminoacetofenona para dar una amida cruda de tipo C (ver el esquema 1)

MS (ES+), m/z = 399,60

Paso 8

De acuerdo con M12, 0,72 g (1,8 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 3,59 g (5 eq.) de

dihidrato de cloruro de estaño para dar 0,132 g (21%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 350,9

^{1}H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (2H, m), 7,4 ppm (3H, m), 7,1 ppm (1H, m), 4,5 ppm (2H, t), 4,0 ppm (2H, d), 2,6 ppm (2H, d), 1,9 ppm (3H, m), 1,6 ppm (5H, m), 1,4 ppm (3H, m), 1,1 ppm (3H, m), 0,9 ppm (2H, m)

EJEMPLO 80

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

(R_1 = isopropilo, R_2 = etilo, R_3 = terc-butilo)

Paso 10

De acuerdo con M13, 0,96 g (3,28 mmol) de 5-terc-butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona reacciona con 0,0984 g de 80% de hidruro de sodio en THF en reflujo durante 1 hora, luego se agrega, a temperatura ambiente, 0,245 ml de yoduro de metilo La mezcla se refluye durante 2 horas para dar 1,14 g del metilsulfanilo G esperado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/acetona) = 0,85

MS (ES+), m/z = 307

Paso 11

1 g (3,26 mmol) del metilsulfanilo G (ver el esquema 1) reacciona con 0,27 g (2 eq) de cianamida para dar 0,825 g (84%) del producto del tipo F esperado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/metanol) = 0,56

punto de fusión 243°C

MS (ES+), m/z = 301

^1H NMR ($CDCl_3$, 400 MHz)

8,6 ppm (1H, bs), 4,5 ppm (2H, q), 3,7 ppm (2H, bs), 3,2 ppm (1H, m), 1,4 ppm (3H, t), 1,3 ppm (6H, d), 1,25 ppm (9H, s)

EJEMPLO 81

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

(R_1 = isopropilo, R_2 = etilo, R_3 = p-tolilo)

Paso 10

De acuerdo con M13, 0,61 g (1,87 mmol) de 1-etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona reacciona con 0,056 g de 80% de hidruro de sodio en THF en reflujo durante 1 hora, luego se agrega, a temperatura ambiente, 0,14 ml de yoduro de metilo La mezcla se refluye durante 2 horas para dar 0,71 g del metilsulfanilo G esperado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/acetona) = 0,78

MS (ES+), m/z = 341

Paso 11

0,64 g (1,87 mmol) del metilsulfanilo G (ver el esquema 1) reacciona con 0,16 g (2 eq) de cianamida para dar 0,43 g (69%) del producto del tipo F esperado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/metanol) = 0,48

punto de fusión 245°C

MS (ES+), m/z = 335

^1H NMR ($CDCl_3$, 400 MHz)

8,86 ppm (1H, bs), 8,0 ppm (2H, d), 7,3 ppm (2H, d), 4,6 ppm (2H, q), 4,15 ppm (2H, bs), 3,3 ppm (1H, m), 2,4 ppm (3H, s), 1,5 ppm (3H, t), 1,4 ppm (6H, d)

EJEMPLO 82

1-Etil-3-isopropil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = etilo, R_3 = 4-metoxifenilo)

Paso 7

De acuerdo con M10, 3,18 g (14 mmol) de ácido 2-etil-5-isopropil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 2,82 g (14 mmol) de clorhidrato de 2-amino-1-(4-metoxifenil)etanona para dar 4,7 g (90%) una amida de tipo C (ver el esquema 1)

MS (ES+), m/z = 375

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, d), 7,7 ppm (1H, t), 7,0 ppm (2H, d), 4,95 ppm (2H, d), 4,25 ppm (2H, q), 3,9 ppm (3H, s), 3,55 (1H, m), 1,5 ppm (3H, t), 1,3 ppm (6H, d)

Paso 8

De acuerdo con M12, 4,7 g (12,5 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 14,2 g de dihidrato de cloruro de estaño para dar 2,84 g (70%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 327

Rf (95/5 de CH_2Cl_2/MeOH) = 0,22

punto de fusión 150°C

^{1}H NMR (DMSO, 400 MHz)

8,25 ppm (1H, t), 8,0 ppm (2H, d), 7,05 ppm (2H, d), 4,45 ppm (2H, q), 4 ppm (2H, d), 3,85 ppm (3H, s), 3,2 ppm (1H, m), 1,35 ppm (3H, t), 1,3 ppm (6H, d)

EJEMPLO 83

Paso 9

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

(R_1 = metilo, R_2 = etilo, R_3 = 4-metoxifenilo)

2,2 g (7,4 mmol) de 1-etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona se refluye en tolueno con 6 g (14,8 mmol) de reactivo de Lawesson para dar 2 g (87%) de un compuesto del tipo E esperado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/metanol) = 0,7

punto de fusión 209°C

MS (ES+), m/z = 315

^1H NMR ($CDCl_3$, 400 MHz)

8,35 ppm (1H, bs), 7,95 ppm (2H, d) 6,95 ppm (2H, d), 6,8 ppm (2H, q), 4,15 ppm (2H, bs), 3,9 ppm (3H, s), 2,4 ppm (3H, s), 1,5 ppm (3H, t)

EJEMPLO 84

1-Etil-3-metil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

(R_1 = metilo, R_2 = etilo, R_3 = 4-metoxifenilo)

Paso 10

De acuerdo con M13, 1,75 g (5,6 mmol) de 1-etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona reacciona con 0,23 g de 60% de hidruro de sodio en THF en reflujo durante 1 hora, luego se agrega, a temperatura ambiente, 0,42 ml de yoduro de metilo La mezcla

se refluye durante 2 horas para dar 2 g (100%) del metilsulfanilo G esperado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/acetona) = 0,86

MS (ES+), m/z = 329

Paso 11

2 g (6,1 mmol) del metilsulfanilo G (ver el esquema 1) reacciona con 0,52 g (2 eq) de cianamida para dar 0,33 g (68%) del producto del tipo F esperado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/metanol) = 0,5

punto de fusión 265°C

MS (ES+), m/z = 323

^1H NMR (DMSO, 400 MHz)

9,45 ppm (1H, bs), 8,1 ppm (2H, d), 7,1 ppm (2H, d), 4,45 ppm (2H, q) 4,15 ppm (2H, bs), 3,85 ppm (3H, s), 2,3 ppm (3H, s), 1,35 ppm (3H, t)

EJEMPLO 85

3-Isopropil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = propilo, R_3 = 4-metoxi-fenilo)

Paso 7

De acuerdo con M10, 3,38 g (14 mmol) de ácido 5-isopropil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 2,82

g (14 mmol) de clorhidrato de 2-amino-1-(4-metoxifenil)etanona para dar 4,58 g (84%) una amida de tipo C (ver el esquema 1)

MS (ES+), m/z = 389

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, d) 7,7 ppm (1H, t), 7,0 ppm (2H, d), 4,95 ppm (2H, d), 4,25 ppm (2H, q), 3,9 ppm (3H, s), 3,55 (1H, m), 1,9 ppm (2H, m), 1,3 ppm (6H, d), 0,95 ppm (3H, t)

Paso 8

De acuerdo con M12, 4,58 g (16 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 13,3 g de dihidrato de cloruro de estaño para dar 2,92 g (73%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 341

^{1}H NMR (DMSO, 400 MHz)

8,2 ppm (1H, t), 8,0 ppm (2H, d), 7,05 ppm (2H, d), 4,4 ppm (2H, q), 4,0 ppm (2H, d), 3,85 ppm (3H, s), 3,2 ppm (1H, m), 1,8 ppm (2H, m), 1,3 ppm (6H, d), 0,85 ppm (3H, t)

Rf (90/10 de CH_2Cl_2/acetona) = 0,37

punto de fusión 142°C

EJEMPLO 86

3-terc-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo R_2 = etilo R_3 = 4-metoxifenilo)

Paso 7

De acuerdo con M10, 3,38 g (14 mmol) de ácido 5-terc-butil-2-etil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 2,82 g (14 mmol) de clorhidrato de 2-amino-1-(4-metoxifenil)etanona para dar 4,92 g (90%) una amida de tipo C (ver el esquema 1)

MS (ES+), m/z = 389

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, d) 7,4 ppm (1H, bs), 7,0 ppm (2H, d), 4,9 ppm (2H, d), 4,2 ppm (2H, q), 3,9 ppm (3H, s), 1,5 (3H, t), 1,4 ppm (9H, s)

Paso 8

De acuerdo con M12, 4,92 g (13 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 14,3 g de dihidrato de cloruro de estaño para dar 2,1 g (49%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 341

Rf (90/10 de CH_2Cl_2/acetona) = 0,32

punto de fusión 180°C

^{1}H NMR (DMSO, 400 MHz)

8,3 ppm (1H, t), 8,0 ppm (2H, d), 7,1 ppm (2H, d), 4,4 ppm (2H, q), 4,0 ppm (2H, d), 3,85 ppm (3H, s), 1,45 ppm (9H, s), 1,35 ppm (3H, t)

EJEMPLO 87

3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = propilo, R_3 = 4-metoxifenilo)

Paso 7

De acuerdo con M10, 3,57 g (14 mmol) de ácido 5-terc-butil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 2,82 g (14 mmol) de clorhidrato de 2-amino-1-(4-metoxifenil)etan na para dar 5 g (89%) una amida de tipo C (ver el esquema 1)

MS (ES+), m/z = 403

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, d), 7,4 ppm (1H, t), 6,95 ppm (2H, d), 4,9 ppm (2H, d), 4,1 ppm (2H, q), 3,9 ppm (3H, s), 1,9 (2H, m), 1,4 ppm (9H, s), 0,9 (3H, t)

Paso 8

De acuerdo con M12, 5 g (12 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 14 g de dihidrato de cloruro de estaño para dar 2,77 g (63%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 355

Rf (90/10 de CH_2Cl_2/acetona) = 0,37

punto de fusión 167°C

^{1}H NMR (DMSO 400 MHz)

8,3 ppm (1H, t), 8,0 ppm (2H, d) 7,1 ppm (2H, d), 4,4 ppm (2H, q), 4,0 ppm (2H, d), 3,85 ppm (3H, s), 1,8 ppm (2H, m), 1,4 ppm (9H, s), 0,85 ppm (3H, t)

EJEMPLO 88

1-Etil-3-metil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

(R_1 = metilo, R_2 = etilo, R_3 = 4-hidroxifenilo)

0,4 g (1,24 mmol) de 1-etil-3-metil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida se refluye en diclorometano con 31 ml de una solución molar de BBr_3 en diclorometano para dar 0,14 g (37%) del producto esperado

MS (ES+), m/z = 309

punto de fusión 300°C

Rf (90/10 de CH_2Cl_2/MeOH) = 0,5

^1H NMR (DMSO, 400 MHz)

10,15 ppm (1H, s), 9,45 ppm (1H, bs), 8,0 ppm (2H, d) 6,9 ppm (2H, d), 4,45 ppm (2H, q), 4,1 ppm (2H, bs), 2,3 ppm (3H, s) 1,35 ppm (3H, t)

EJEMPLO 89

(±)3-sec-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = sec-butilo, R_2 = etilo, R_3 = 4-metoxifenilo)

2/3

Paso 7

De acuerdo con M10, 3,38 g (14 mmol) de ácido 2-etil-5-sec-butil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 2,82 g (14 mmol) de clorhidrato de 2-amino-1-(4-metoxifenil)etanona para dar 4,69 g (86%) una amida de tipo C (ver el esquema 1)

MS (ES+), m/z = 389

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, d), 7,7 ppm (1H, t), 7,0 ppm (2H, d), 4,95 ppm (2H, d), 4,3 ppm (2H, q), 3,9 ppm (3H, s), 3,4 (1H, m), 1,85 ppm (1H, m), 1,65 ppm (1H, m), 1,5 ppm (3H, t), 1,3 ppm (3H, d) 0,9 ppm (3H, t)

Paso 8

De acuerdo con M12, 4,69 g (12 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 13,6 g de dihidrato de cloruro de estaño para dar 2,85 g (69%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 341

^{1}H NMR (DMSO, 400 MHz)

8,25 ppm (1H, t), 8 ppm (2H, d), 7,05 ppm (2H, d), 4,45 ppm (2H, q), 4 ppm (2H, d), 3,8 ppm (3H, s), 3 ppm (1H, m), 1,75 ppm (1H, m), 1,65 ppm (1H, m), 1,35 ppm (3H, t), 1,25 ppm (3H, d), 0,8 ppm (3H, t)

Rf (90/10 de CH_2Cl_2/acetona) = 0,29

punto de fusión 50°C

EJEMPLO 90

(±)3-sec-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = sec-butilo, R_2 = propilo, R_3 = 4-metoxi-fenilo)

Paso 7

De acuerdo con M10, 3,57 g (14 mmol) de ácido 5-sec-butil-4-nitro-2-propil-2H-pirazol-3-carboxílico (A) reacciona con 2,82 g (14 mmol) de clorhidrato de 2-amino-1-(4-metoxifenil)etanona para dar 4,77 g (85%) una amida de tipo C (ver el esquema 1)

MS (ES+), m/z = 403

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (2H, d), 7,7 ppm (1H, t), 7,0 ppm (2H, d), 4,95 ppm (2H, d), 4,2 ppm (2H, q), 3,9 ppm (3H, s), 3,4 ppm (1H, m), 1,9 ppm (3H, m), 1,6 ppm (1H, m), 1,3 (3H, d), 0,9 ppm (6H, m)

Paso 8

De acuerdo con M12, 4,77 g (12 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 13,4 g de dihidrato de cloruro de estaño para dar 2,37 g (56%) del producto D esperado (ver el esquema 1)

Rf (90/10 de CH_2Cl_2/acetona) = 0,37

punto de fusión 85°C

MS (ES+), m/z = 355

^{1}H NMR (DMSO, 400 MHz)

8,25 ppm (1H, t), 8,0 ppm (2H, d), 7,05 ppm (2H, d), 4,4 ppm (2H, q), 4,0 ppm (2H, m), 3,8 ppm (3H, s), 3,0 ppm (1H, m), 1,75 ppm (3H, m), 1,65 ppm (1H, m), 1,25 ppm (3H, d), 0,8 ppm (6H, m)

EJEMPLO 91

1-Etil-3-metil-5-(3,4,5-trimetoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo R = 3,4,5-trimetoxifenilo)

Paso 7

De acuerdo con M10, 3,153 g (0,77 mmol) de ácido 2-etil-5-metil-4-nitro-2H-pirazol-3-carboxílico (A) reacciona con 2,246 g (0,77 mmol) de clorhidrato de 2-amino-1-(3,4,5-trimetoxifenil)etanona (78%) (J Org Chem , 38, 3571-3575, 1973) para dar 0,313 g (83%) una amida de tipo C (ver el esquema 1)

Rf (CH_2Cl_2/MeOH 95/5) = 0,78

^{1}H NMR ($CDCl_3$, 400 MHz)

8,0 ppm (1H, bs), 7,2 ppm (2H, d), 5,0 ppm (2H, d), 4,3 ppm (2H, q), 3,9 ppm (9H, s), 2,6 ppm (3H, s) 1,5 ppm (3H, t)

Paso 8

De acuerdo con M12, 0,26 g (0,64 mmol) de la amida C (ver el esquema 1) se refluye en etanol con 0,72 g de dihidrato de

cloruro de estaño para dar 0,13 g (57%) del producto D esperado (ver el esquema 1)

Rf (95/5 de CH_2Cl_2/MeOH) = 0,52

punto de fusión 208°C

MS (ES+), m/z = 359

^1H NMR (DMSO, 400 MHz)

8,25 ppm (1H, t), 7,3 ppm (2H, s), 4,45 ppm (2H, q) 4,0 ppm (2H, d), 3,9 ppm (6H, s), 3,7 ppm (3H, s), 2,3 ppm (3H, s), 1,35 ppm (3H, t)

EJEMPLO 92

1-Etil-5-(3-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 3-hidroxifenilo)

0,4 g (1,34 mmol) de 1-etil-5-(3-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona se refluye en diclorometano con 33,5 ml de una solución molar de BBr_3 en diclorometano para dar 0,075 g (20%) del producto esperado

MS (ES+), m/z = 285

punto de fusión 204°C

Rf (90/10 de CH_2Cl_2/MeOH) = 0,55

^1H NMR (DMSO, 400 MHz)

9,65 ppm (1H, s) 8,25 (1H, m), 7,45 ppm (2H, m) 7,33 ppm (1H, m), 6,9 ppm (1H, m), 4,4 ppm (2H, q), 3,95 ppm (2H, d), 2,3 ppm (3H, s) 1,35 ppm (3H, t)

212

EJEMPLO 93

1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo, R_3 = 2-hidroxifenilo)

0,4 g (1,34 mmol) de 1-etil-5-(2-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona se refluye en diclorometano con 33,5 ml de una solución molar de BBr_3 en diclorometano para dar 0,070 g (19%) del producto esperado

MS (ES+), m/z = 285

punto de fusión 220°C

Rf (90/10 de CH_2Cl_2/MeOH) = 0,7

^{1}H NMR (DMSO, 400 MHz)

14,0 ppm (1H, s), 8,35 (1H, m), 7,8 ppm (1H, m), 7,4 ppm (1H, m), 7,0 ppm (2H, m), 4,45 ppm (2H, q), 4,2 ppm (2H, d), 2,3 ppm (3H, s), 1,35 ppm (3H, t)

EJEMPLO 94

1-Etil-5-(4-hidroxifenil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = etilo, R_3 = 4-hidroxifenilo)

0,5 g (1,53 mmol) de 1-etil-5-(4-metoxifenil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona se refluye en diclorometano con 38 ml de una solución molar de BBr_3 en diclorometano para dar 0,23 g (48%) del producto esperado

MS (ES+) m/z = 313

213

punto de fusión 230°C

Rf (90/10 de CH_2Cl_2/MeOH) = 0,27

^1H NMR (DMSO, 400 MHz)

10,0 ppm (1H, s) 8,2 (1H, t), 7,85 ppm (2H, d), 6,85 ppm (2H, d), 4,4 ppm (2H, q), 3,9 ppm (2H, d), 3,2 ppm (1H, m), 1,35 ppm (3H, t), 1,3 ppm (6H, d)

EJEMPLO 95

5-(4-Hidroxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = propilo R_3 = 4-hidroxifenilo)

0,5 g (1,47 mmol) de 5-(4-metoxifenil)-3-isopropil-1-propil-5,6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona se refluye en diclorometano con 37 ml de una solución molar de BBr_3 en diclorometano para dar 0,2 g (42%) del producto esperado

MS (ES+), m/z = 327

punto de fusión 230°C

Rf (90/10 de CH_2Cl_2/MeOH) = 0,38

^1H NMR (DMSO, 400 MHz)

10,0 ppm (1H, s), 8,2 (1H, t), 7,85 ppm (2H, d), 6,85 ppm (2H, d), 4,4 ppm (2H, q), 3,9 ppm (2H, d), 3,2 ppm (1H, m), 1,8 ppm (2H, m) 1,3 ppm (6H, d) 0,85 ppm (3H, t)

EJEMPLO 96

5-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = terc-butilo, R_2 = etilo, R_3 = 4-hidroxifenilo)

0,5 g (1,47 mmol) de 1-terc-butil-5-(4-metoxifenil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona se refluye en diclorometano con 1,4 ml de BBr_3 en diclorometano para dar 0,29 g (60%) del producto esperado

MS (ES+), m/z = 327

punto de fusión 264°C

Rf (90/10 de CH_2Cl_2/MeOH) = 0,4

^{1}H NMR (DMSO, 400 MHz)

10,0 ppm (1H, s), 8,2 (1H, t), 7,85 ppm (2H, d), 6,85 ppm (2H, d), 4,4 ppm (2H, q), 3,9 ppm (2H, d), 1,4 ppm (9H, s), 1,3 ppm (3H, t)

EJEMPLO 97

3-Etoximetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = etoximetilo, R_2 = etilo, R_3 = fenilo)

Paso 19

8,1 g (22 mmol) del compuesto R (ver el esquema 3) reaccionan con 49 ml de etilenglicol y 0,81 g (4,3 mmol) de ácido para-toluensulfónico monohidratado en 170 ml de tolueno. A las 48

215 220

horas, se han removido aproximadamente 40 ml de agua (aparato de Dean-Stark) La mezcla de la reacción se trata con una solución de $NaHCO_3$ saturado y agua y luego se deja que las fases se separen mediante asentamiento La fase orgánica se seca sobre Na_2SO_4 y se concentra El aceite obtenido es sometido a cromatografía sobre sílice con una mezcla de 80/20 de ciclohexano/EtOAc para dar 6,6 g (73%) del compuesto S esperado (ver el esquema 3)

Fr (70/30 de ciclohexano/EtOAc) = 0,28

MS (ES+), m/z = 418,9

^1H NMR ($CDCl_3$, 400 MHz)

7,3-7,55 ppm (6H, m), 4,4-4,5 ppm (4H, m), 4,1 ppm (2H, q), 3,8 ppm (4H, m), 1,5 ppm (3H, t), 1,4 ppm (3H, t)

Paso 20

1,5 g (3,6 mmol) del compuesto S (ver el esquema 3) reaccionan con 4,3 ml (8,6 mmol) de una solución 2M de borohidruro de litio en THF, en 25 ml de THF anhidro Después de 12 horas a temperatura ambiente, la mezcla de la reacción se extrae con agua y éter dietílico La fase orgánica se seca sobre Na_2SO_4 y se concentra para dar 1,2 g (96%) del compuesto T esperado (ver el esquema 3)

Rf (95/5 de CH_2Cl/MeOH) = 0,17

MS (ES+), m/z = 347

^1H NMR (DMSO 400 MHz)

8,65 ppm (1H, m), 7,3-7,5 ppm (5H, m), 4,9 ppm (1H, t), 4,4 ppm (2H, d), 4,3 ppm (2H, q), 4,05 ppm (2H, t), 4,0 ppm (2H, s), 3,8 ppm (2H, t) 3,7 ppm (2H, d), 1,2 ppm (3H, t)

Paso 21

0,3 g (0,9 mmol) del compuesto T (ver el esquema 3) se extrae con 15 ml de etanol y 15 ml de HCl 6N a 80°C Después de 12 horas, la mezcla de la reacción se concentra y el residuo obtenido se extrae con agua y diclorometano La fase orgánica se seca sobre Na_2SO_4 y se concentra y luego es sometida a cromatografía sobre sílice usando un gradiente de elución desde el 100% de diclorometano hasta una mezcla de 95/5 de diclorometano/MeOH, para dar 0,023 g (8,5%) del compuesto D (ver el esquema 3) (RB = etilo)

Rf (95/5 de CH_2Cl_2/MeOH) = 0,27

MS (ES+), m/z = 313

^{1}H NMR ($CDCl_3$, 400 MHz)

7,9 ppm (2H, m), 7,45 ppm (3H, m), 6,0 ppm (1H, m), 4,75 ppm (2H, s), 4,6 ppm (2H, q), 4,15 ppm (2H, d), 3,65 ppm (2H, q), 1,5 ppm (3H, t), 1,25 ppm (3H, t)

EVALUACIÓN DE LA ACTIVIDAD BIOLÓGICA DE LOS COMPUESTOS DE LA PRESENTE INVENCION

Evaluación de la actividad *in vitro* de los compuestos de l s ejemplos

La capacidad de los compuestos de la fórmula (I) de la invención de inhibir las fosfodiesterasas de nucleótidos cíclicos se evalúa midiendo su IC_{50} (la concentración necesaria para inhibir el 50% de la actividad enzimática) En el caso de las enzimas PDE4, este valor se compara con el valor de IC_{50} para rolipram, un inhibidor de referencia para las enzimas PDE4

Las fosfodiesterasas de tipo 4 se obtienen de una preparación citosólica extraída de una cadena de células de origen humano, U937, de acuerdo con el método adaptado de T J Torphy et al, 1992, J Pharm Exp Ther 263 1195-1205

Los otros tipos de fosfodiesterasa se obtienen durante la purificación parcial mediante FPLC en una columna de Mono Q (columna de intercambio de aniones) de acuerdo con un método adaptado de Lavan B E , Lakey T , Houslay M D Biochemical Pharmacology, 1989, 38(22), 4123-4136, y Silver P J et al, 1988 Eur J Pharmacol 150 85-94 comenzando con cadenas de

células de origen humano para PDE1 (cadena de monocitos TPH1) y PDE5 (cadena derivada de un adenocarcinoma MCF7), o comenzando con una aorta de perro para PDE3, o, para PDE3A humana, comenzando con una clonación de genes en células de insectos SF21 en baculovirus, de acuerdo con el método adaptado de Luckow, V A et al, 1991, en Tecnología del ADN Recombinante y Aplicaciones, eds Prokop, Bajpai, R K & Ho, C S , páginas 97-152

La medición de la actividad enzimática para los diversos tipos de PDE, y en particular las enzimas PDE4, se lleva a cabo de acuerdo con un método adaptado de W J Thomson et al, 1979, Avances en La investigación de los Nucleótidos Cíclicos, Volumen 10 69-92, ed G Brooker et al, Raven Press, NY

Para la determinación del valor de IC_{50}, la actividad enzimática se mide en la presencia del inhibidor en una gama de concentración de 0,1 a 100 µM

La Tabla 1 siguiente ilustra la actividad inhibidora de PDE4 coparada con la de rolipram en una preparación de enzimas obtenida de la cadena de U937

Tabla 1

Ejemplo	IC_{50} (μM)	Ejemplo	IC_{50} (μM)	Ejemplo	IC_{50} (μM)	Ejemplo	IC_{50} (μM)
1	0,0049	25	0,0024	50	0,016	75	0,0049
2	0,00098	26	0,0056	51	0,06	76	0,0082
3	0,00012	27	0,0038	52	0,00065	77	0,21
4	0,0084	28	0,090	53	0,26	78	0,021
5	0,39	29	0,33	54	0,24	79	0,011
6	0,42	30	0,30	55	0,0017	80	0,00022
7	0,13	31	0,19	56	0,50	81	0,00054
8	0,21	32	0,13	57	0,00013	57	0,062
9	0,15	33	0,11	58	0,14	83	0,10
10	1,29	34	0,0047	59	0,51	84	0,060
11	0,12	35	0,00070	60	0,58	85	0,20
12	0,10	36	0,00039	61	0,0079	86	0,31
13	0,13	37	0,00097	62	0,26	87	0,041
14	0,081	38	0,65	63	0,0050	88	0,0021
15	0,52	39	0,0091	64	0,0046	89	0,033
16	0,42	40	0,0082	65	0,0015	90	0,193
17	0,0059	41	0,011	66	0,00063	91	0,90
18	0,10	42	0,010	67	0,0010	92	0,092
19	0,087	43	0,048	68	0,0062	93	0,0074
20	0,099	44	0,0011	69	0,013	94	0,0021
21	0,0026	45	0,0026	70	0,011	95	0,015

22	0,028	46	0,00084	71	0,035	96	0,0049
23	0,042	47	0,021	72	0,0018	97	1,58
24	0,078	48	0,0081	73	0,00073		
		49	0,032	74	0,0054	Rolipram	0,859

El examen de los resultados de la Tabla 1 muestra que los productos de la invención ensayados en el estudio generalmente inhiben la enzima PDE4 de origen humano mucho más efectivamente que rolipram, y en ciertos casos estos productos son entre 3 000 y 4 000 más activos que rolipram

Evaluación de la actividad *in vitro* de los compuestos de la invención

Modelo de TNFα en vivo en ratas Wistar

TNFα es una citoquina que juega un papel central en los mecanismos de inflamación Su producción puede ser inducida por una inyección de lipopolisacárido (LPS) Se ha mostrado que el aumento en el cAMP intracelular, producido en particular por los inhibidores de PDE4, disminuye la producción de TNFα en modelos *in vitro* y en vivo Entonces es cuestión aquí de cuantificar en vivo el potencial antiinflamatorio de los compuestos de la invención, administrados por vía oral midiendo la inhibición de la

producción de TNFα en el plasma de ratas, estas ratas han recibido una inyección intraperitoneal de lipoplisacárido (LPS) El tratamiento cn los compuestos de la invención o el vehículo se administra por vía oral a ratas Wistar machos, 30 minutos antes de la inyección de LPS Las ratas son sacrificadas 90 minutos después de la estimulación LPS, se recoge la sangre en EDTA y se mide la concentración de TNFα en cada muestra de plasma La mayor parte de los compuestos de la invención y en particular los compuestos siguientes mostraron excelente actividad en este modelo

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-(2-Hidroxietil)-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

222 22x

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,]diazepin-8-ona,

1-Etil-3-metil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(3-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-Ciclohexil-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-metil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazol[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)-benzonitrilo,

5-(2,4-Dimetoxifenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidro-pirazolo-[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidropirazolo-[4,3-e][1,4]diazepin-5-il)benzonitrilo,

1-Etil-3-metil-5-fenil-1,6-dihidropirazolo-[4,3-e][1,4]diazepin-8-ilcianamida,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

(±)3-sec-Butil-1-etil-5-fenil-6,7-dihdidro-1H-pirazolo-[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

224 2/9

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

Referencias

Chen, Y L , Le Vraux, V , Giroud, J P y Chauvelot-Moachon L (1994) Propiedades de factor de necrosis antitumor de drogas que no contienen péptidos en las respuestas de fase aguda Eur J Pharmacol , 271 (2-3), 319-27

Prabhakar, U , Lipshutz, D , O'Leary Barthus, J , Slivjak, J Smith III E F , Lee, J C y Esser K M (1994), Caracterización de la inhibición dependiente del cAMP de la producción de TNFa inducida por LPS por rolipram, un inhibidor de la fosfodiesterasa específica IV (PDE IV) Int J Immunopharmacol , 16(10), 805-816

Modelo de eosinofilia en ratas

Los estudios realizados usando este modelo experimental tienen el objetivo de evaluar la actividad inhibidora de los compuestos de la invención en el aflujo de células inflamatorias, en particular de los eosinófilos en el lavado

del sistema broncotraqueal de las ratas Los eosinófilos juegan un papel principal en la fisiopatología del asma en el hombre al liberar en el parénquima pulmonar, mediadores proinflamatorios tales como los leucotrienos, proteínas y enzimas específicas (ECP, EPO, MBP) y citoquinas El reclutamiento masivo de este tipo de células en las vías respiratorias de un asmático lleva a una degradación gradual del tejido pulmonar, que explica la hiperreactividad bronquial, el aspecto crónico de la enfermedad y las exacerbaciones cuando no hay tratamiento Este modelo usa ratas Brown Norway, que tienen la característica particular de producir, como los pacientes atópicos, altos niveles de inmunoglobulina E (IgE) en respuesta a una sensibilización por un antígeno El protocolo usado incluye dos sensibilizaciones con ovalbúmina con un intervalo de catorce días, seguido por una administración siete días más tarde de una aspersión de ovalbúmina 48 Horas después de administración de antígenos, los animales son sometidos a un lavaje broncoalveolar con anestesia para recoger la infiltración de células pulmonares en los pulmones Estas células luego se cuentan y se diferencian de acuerdo con criterios morfológicos Los productos de la invención se administran por vía oral, 1 hora antes de la administración de antígenos La mayor parte de los compuestos de la presente invención ensayados en este modelo también demostraron excelente actividad

Referencias

Corrigan et al (1992) Inmunología hoy 13 501-507

Elwood et al (1995) Inflam Res 44 83-86

Modelo de neutrofilia en ratones

Los estudios realizados usando este protocolo experimental tienen el objetivo de evaluar la acción moduladora de los compuestos de la invención sobre el aflujo de células pro-inflamatorias (primera fase) en el lumen del sistema broncotraqueal de los ratones Este aflujo celular sigue una estimulación que imita una infección bacteriana (lipopolisacárido bacteriano o LPS) Esta primera etapa inflamatoria es el resultado de una combinación de hechos, los principales de los cuales son la síntesis y la liberación de factores estimuladores ($TNF\alpha^{i}$) y factores quimiotácticos ($IL-8^{ii}$), el aumento en la permeabilidad vascular en la microcirculación broncotraqueal y la infiltración de los neutrófilos polimorfonucleares^{iii} concomitante con la exudación de proteínas plasmáticas en los tejidos pulmonares

Este proceso patológico se halla en la bronconeumopatía obstructiva crónica (o COPD), en la cual el neutrófilo, en concierto con el macrófago, juega un papel clave en la

propios neutrófilos, pero también en la obstrucción de los tejidos pulmonares (disminución en las funciones pulmonares), la hipersecreción de la mucosa broncotraqueal (congestión de las vías respiratorias), inflamación del tejido (liberación de mediadores inflamatorios y radicales libres) y aumento en la tonicidad basal de las fibras de los músculos lisos pulmonares (gen respiratorio crónico) La myor parte de los compuestos de la presente invención ensayados en este modelo demostraron excelente actividad

Referencias

[i] SUTER P M , SUTER S , GIRARDIN E , ROUX-LOMBARD P , GRAU G E y DAVER J -M 1992 Los altos niveles broncoalveolares del factor de necrosis de tumores y sus inhibidores, interleucina-1-, interferona y elastasa, en pacientes con síndrome de insuficiencia respiratoria de adultos después de un trauma, shock o sepsis Am Rev Respir Dis 145 1016-1022

[ii] MARTIN T R y GOODMAN R B 1999 El papel de las quimioquinas en la patología del síndrome de insuficiencia respiratoria aguda Capítulo 6 en Quimioquinas en enfermedades Biología e investigación clínica editado por C A Hébert, Humana Press Inc , Totowa, NJ

[iii] REPINE J E y BEEHLER C J 991 Los neutrófilos y el síndrome de insuficiencia respiratoria adulta dos perspectivas entrelazadas

Inflamación yeyunal y ataque séptico inducido por el lipopolisacárido de E coli en ratas

El lipopolisacárido (LPS) de Escherichia coli administrado por vía intravenosa a ratas Wistar machos en ayunas induce una inflamación del yeyuno dos horas más tarde

En estos experimentos se usan ratas Wistar machos (200 g - 280 g), en ayunas (18 horsa), de Sté Janvier, Le-genest-St Isle, Mayenne, Francia

Los compuestos que se han de ensayar se suspenden en un vehículo (1% de metilcelulosa (95% v/v) + polietilenglicol 40 (5% v/v)) Luego se administran por vía oral (5 ml/kg) usando una sonda de acero inoxidable, una hora antes de la administración del agente inductor (LPS) Los grupos de animales se distribuyen de la siguiente manera

- Controles negativos vehículo por vía oral + solución salina fisiológica intravenosa en suero
- Controles positivos vehículo por vía oral + LPS

- Tratado compuesto por vía oral + LPS

El lipopolisacárido (LPS), endotoxina de Escherichia coli (serotipo 0127 B8), se inyecta luego por vía intravenosa (vena caudal) a una dosis de 40 mg/kg (5 ml/kg) a ratas concientes mantenidas con un apoyo liviano

Dos horas más tarde, los animales son sacrificados, se abre el abdomen y se toma una sección de 10 cm del yeyuno (trigésimo al cuadragésimo después del píloro), se corta en la dirección de su longitud, se lo seca y se lo pesa

Se evalúa el ataque macroscópico (0 = ninguno, 1 = ligero, 2 = moderado, 3 = grave)

Después de pesarlo, se fija el segmento sobre una superficie plana y se realizan las mediciones del porcentaje de superficies hiperhemiadas usando un analizador de imágenes

Inmediatamente después del análisis, el tejido se deposita en 10 ml de reactivo de Drabkin para determinar el contenido de hemoglobina del tejido (ensayo colorimétrico 24 horas más tarde) La mayor parte de los compuestos de la presente invención ensayados en este modelo demostraron excelente actividad

230

Lipopolisacárido (LPS) Sigma, referencia L-3880, Francia

Polietilenglicol Peso molecular 400, Sigma, referencia P-3265

Contenido de hemoglobina del yeyuno Kit de Sigma, Hemoglobina Total, referencia 525-A

Referencia principal

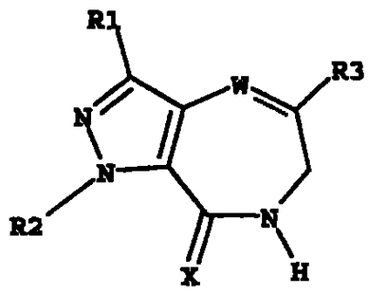
Cardelus Ignasi et al European Journal of Pharmacology 299 (1996), 153-159

231

REIVINDICACIONES

Habiendo descripto y determinado la naturaleza y alcance de la presente invención y la manera en que la misma ha de ser llevada a la práctica, se declara que lo que reivindica como invención y de propiedad exclusiva es

1 Un compuesto de la fórmula I siguiente



I

en donde

R_1 se elige de los siguientes grupos

hidrógeno,

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono

cicloalquilo que contiene de 3 a 6 átomos de carbono,

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de

nitrógeno, oxígeno, az fre

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nC(S)R_B$, $(CH_2)_nC(S)OR_B$, $(CH_2)_nC(S)SR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, $(CH_2)_nNR_DC(O)NR_DR_B$ o $(CH_2)_nZ$, en donde

R_A se elige de alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono

cicloalquilo que contiene de 3 a 6 átomos de carbono,

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,
alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

R_B y R_C, que pueden ser idénticos o diferentes, se eligen de hidrógeno,
alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono
cicloalquilo que contiene de 3 a 6 átomos de carbono,
alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,
arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,
arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,
alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

siendo posible que R_B y R_C formen un anillo que contiene de 5 a 7 átomos de carbono que pueden incluir uno o más heteroátomos elegidos de S, N y O

R_D es hidrógeno o alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

Z es un halógeno, y

n es un número entero de 0 a 4 inclusive,

R_2 se elige de los siguientes grupos

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

cicloalquilo que contiene de 3 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

235 240

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_mOR_B$, $(CH_2)_mCF_3$, $(CH_2)_mC(O)R_B$, $(CH_2)_mCOOR_B$, $(CH_2)_mOC(O)R_A$, $(CH_2)_mSR_B$, $(CH_2)_mC(S)R_B$, $(CH_2)_mC(S)OR_B$, $(CH_2)_mC(S)SR_B$, $(CH_2)_mNR_BR_C$, $(CH_2)_mC(O)NR_BR_C$, $(CH_2)_mNR_CC(O)R_B$, $(CH_2)_mNR_DC(O)NR_DR_B$ o $(CH_2)_mZ$, en donde

R_A, R_B, R_C, R_D y Z son lo definido anteriormente,

y m es un número entero de 1 a 4 inclusive,

n es un número entero de 0 a 4 inclusive

R_3 se elige de los siguientes grupos

hidrógeno,

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

cicloalquilo que contiene de 3 a 6 átomos de carbono,

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

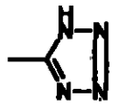
alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nC(S)R_B$, $(CH_2)_nC(S)OR_B$, $(CH_2)_nC(S)SR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, $(CH_2)_nNR_DC(O)NR_DR_B$ o $(CH_2)_nZ$, en donde

R_A, R_B, R_C, R_D y n son lo definido anteriormente,

los grupos arilo, arilalquilo, y alquilarilo definidos anteriormente son no sustituidos o sustituidos en el grupo arilo con 1, 2, o 3 grupos elegidos de

halógeno, hidroxilo, NO, NO_2, CN, alcoxi que contiene de 1 a 4 átomos de carbono, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, $(CH_2)_nHNSO_2R_B$, $(CH_2)_nN(SO_2R_B)_2$, CO_2R_B, CF_3 y



en donde R_B, R_C y n son lo definido anteriormente, y

la línea de puntos presente en la fórmula I indica que la unión entre W y el carbono en la posición 5 puede ser

- una sola unión, en cuyo caso W representa un átomo de nitrógeno sustituido con un átomo de hidrógeno,
- una unión doble, y en este caso W representa un átomo de carbono no sustituido,

X es S, O, N-CN o N-R_8 en donde R_8 es lo definido anteriormente

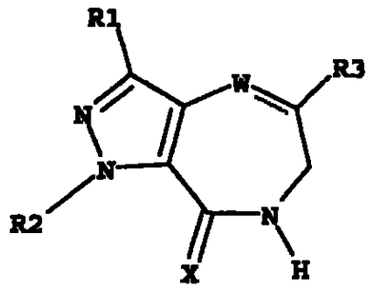
así como los óxidos, las formas tautómeras y los isómeros ópticos correspondientes o los derivados farmacéuticamente aceptables de los compuestos de la fórmula I, con la salvedad de que cuando

R_1 representa un grupo metilo, R_2 un grupo etilo, W es N, X es un átomo de oxígeno y la unión entre W y el átomo de carbono en la posición 5 es una unión doble,

entonces

R_3 no es ni un grupo fenilo no sustituido ni un grupo fenilo que lleva un átomo de flúor en una posición orto como único sustituyente

2 Compuestos de la fórmula I siguiente



I

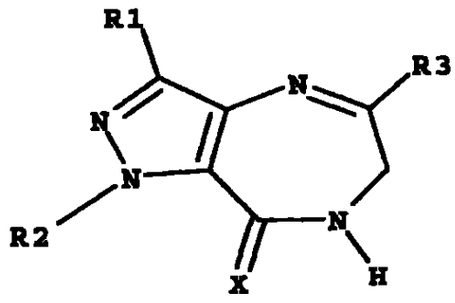
en donde R_1, R_2, R_3 y X son lo definido en la reivindicación 1, W representa un átomo de nitrógeno no sustituido y la unión entre W y el carbono en la posición 5, simbolizada por ═══, es una union doble,

así como los óxidos, las formas tautómeras y los isómeros ópticos correspondientes o los derivados farmacéuticamente aceptables de los compuestos de la fórmula I, con la salvedad de que cuando

R_1 representa un grupo metilo, R_2 un grupo etilo, W es N, X es un átomo de oxígeno y la unión entre W y el átomo de carbono en la posición 5 es una unión doble, entonces

R_3 no es ni un grupo fenilo no sustituido ni un grupo fenilo que lleva, como único sustityente, un átomo de flúor en una posición orto

3 Un compuesto de acuerdo con la reivindicación 1 o 2, de la fórmula II siguiente



II

en donde

R_1 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

un grupo alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono

un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, o $(CH_2)_nZ$, en donde

R_A se elige de alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

cicloalquilo que contiene de 3 a 6 átomos de carbono,

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono

R_B y R_C, que pueden ser idénticos o diferentes, se eligen de hidrógeno,

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

cicloalquilo que contiene de 3 a 6 átomos de carbono

alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono

R_B y R_C posiblemente forman un anillo que contiene de 5 a 7 átomos que pueden incluir uno o más heteroátomos elegidos de S, N u O,

Z es un halógeno y

n es un número entero de 0 a 4 inclusive,

R_2 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

$(CH_2)_nCF_3$, en donde n es un número entero de 0 a 4 inclusive,

metilciclopropilo,

alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

o un grupo $(CH_2)_mOR_8$ y $(CH_2)_mCO_2R_8$, en donde m es un número entero de 1 a 3 inclusive y R_8 es lo descripto anteriormente,

R_3 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

un grupo alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

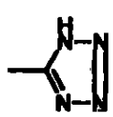
un grupo alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono,

los grupos $(CH_2)_nOR_B$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$ y $(CH_2)_nNR_CC(O)R_B$, en donde

R_A, R_B, R_C, R_D y n son lo definido anteriormente,

los grupos arilo, arilalquilo, y alquilarilo definidos anteriormente son no sustituidos o sustituidos en el grupo arilo con 1, 2, o 3 grupos elegidos de

halógeno, hidroxilo, NO, NO_2, CN, alcoxi que contiene de 1 a 4 átomos de carbono, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, $(CH_2)_nHNSO_2R_B$, $(CH_2)_nN(SO_2R_B)_2$, CO_2R_B, CF_3 y



en donde R_B, R_C y n son lo definido anteriormente, y X es O, S o NCN

244 249

4 Un compuesto de acuerdo con la reivindicación 1 o 2, caracterizado porque

R_1 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono

un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

un grupo alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 6 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo alquenilo lineal o ramificado que contiene de 2 a 6 átomos de carbono

los grupos $(CH_2)_nOR_B$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, o $(CH_2)_nZ$, en donde

R_A se elige de alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono,

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

R_B y R_C, que pueden ser idénticos o diferentes, se eligen de hidrógeno,

alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono

arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

n es un número entero de 0 a 4 inclusive,

R_2 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono o un grupo $(CH_2)_mOH$ o $(CH_2)_mCO_2H$, en donde m es un número entero de 1 a 3 inclusive,

R_3 es un grupo alquilo lineal o ramificado que contiene de 1 a 6 átomos de carbono

246 24

un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

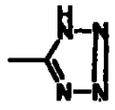
un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo arilalquilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

un grupo alquilarilo que contiene de 6 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre,

los grupos arilo, arilalquilo, y alquilarilo definidos anteriormente son no sustituidos o sustituidos en el grupo arilo con 1, 2, o 3 grupos elegidos de

halógeno, hidroxilo, NO, NO_2, CN, alcoxi que contiene de 1 a 4 átomos de carbono, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, CO_2R_B, CF_3 y



en donde R_B, R_C y n son lo definido anteriormente, y X es O, S, o NCN

5 Un compuesto de acuerdo con la reivindicación 1 o 2, caracterizado porque

R_1 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono

un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono

un grupo alquilcicloalquilo que comprende un grupo alquilo que contiene de 1 a 3 átomos de carbono y un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono,

R_2 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono,

R_3 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono,

un grupo arilo que contiene de 5 a 10 átomos de carbono, optativamente interrumpido con un heteroátomo elegido de nitrógeno, oxígeno y azufre, preferentemente fenilo o piridilo, los grupos arilo son no sustituidos o sustituidos con 1, 2, o 3 grupos, que pueden ser idénticos o diferentes, elegidos de NH_2, halógeno, metoxi, hidroxilo, CN, CH_3 y CF_3, y

X es O, S o NCN

6 Un compuesto de acuerdo con la reivindicación 1 o 2, caracterizado porque

R_1 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono

R_2 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono o un grupo $(CH_2)_nOH$, en donde n es un número entero de 1 a 4 inclusive,

R_3 es un grupo alquilo lineal o ramificado que contiene de 1 a 4 átomos de carbono, un grupo cicloalquilo que contiene de 3 a 6 átomos de carbono, un grupo arilo elegido de fenilo y tienilo, que puede ser no sustituido o sustituido con un grupo elegido de halógeno, hidroxilo, metoxi, NH_2 y CH_3 y

X es S u O

7 Un compuesto de acuerdo con las reivindicaciones 1 a 6, elegido del grupo formado por

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(4-Bromofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1,3-Dimetil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Metoxifenil)-1,3-dimetil-6,7-dihidro-1H-pirazolo[4,3-e][2,4]diazepin-8-ona

5-(4-Bromofenil)-1,3-dimetil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

249 256

1-Etil-3-metil-5-naft-2-il-6,7-dihidro-1-H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(3-Clorotien-2-il)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

Metil 3-(1-etil-3-metil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)propanoato,

1-Etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Clorofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(4-fluorofenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(3-Bromofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Isopropil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)1-Etil-3-metil-5-fenil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-(2-Hidroxietil)-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(3-metoxipropil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(2-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(2-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-fenil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona, isómero 1,

1-Etil-3-metil-5-fenil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona, isómero 2,

3-Metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-metil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(3-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-3-metil-1-propil-6,7-dihidro-1H-pirazolo[4,3-1][1,4]diazepin-8-ona,

3-Metil-5-fenil-1-(2,2,2-trifluoroetil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1,5-Dietil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-Ciclohexil-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(±)1-Etil-3-metil-5-pirid-4-il-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-metil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Dietilaminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

N-[4-(1-Etil-3-metil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)fenil]acetamida,

4-(1-Etil-3-metil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)-benzonitrilo

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

1-Etil-3-isopropil-5-(4-pirrolidin-1-il-fenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(2,4-Dimetoxifenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

3-Isopropil-1-propil-5-(4-pirrolidin-1-il-fenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(2,4-Dimetoxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3,5-Di-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3-terc-Butil-1-etil-5-(4-pirrolidin-1-il-fenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-5-(2,4-dimetoxifenil)-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-=pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-terc-Butil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3-terc-Butil-1-propil-5-(4-pirrolidin-1-il-fenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-5-(2,4-dimetoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-metil-5-pirid-3-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-metil-5-pirid-2-il-6,7-dihidro-1H-piraozlo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-ilcianamida,

N-[4-(1-Etil-3-metil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)fenil]-(fenilsulfonil)bencensulfonamida,

(1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-il)metilamina,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-piraozlo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Ciclopentil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Ciclopropilmetil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Ciclobutilmetil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Alil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

255 - 260

1-Etil-3-metil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-isopropil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

(±)3-sec-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(±)3-sec-Butil-5-fenil-1-propil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

256 261

3-Ciclohexil-1-etil-5-fenil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-5-fenil-1-propil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][2,4]diazepin-8-ona,

3-Ciclohexilmetil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

Etil éster del ácido 1-etil-8-oxo-5-fenil-1,6,7,8-tretrahidropirazolo[4,3-e][1,4]diazepin-3-carboxílico,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidenciamida

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-Isopropil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

(±)3-sec-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(±)3-sec-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-metil-5-(3,4,5-trimetoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(3-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-(2,3,4-trimetoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3,5-difenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Hidroxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(2,6-Dimetoxifenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Etoximetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

8 Un compuesto de acuerdo con las reivindicaciones 1 a 6, elegido del grupo formado por

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(4-Bromofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-naft-2-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(3-Clorotien-2-il)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

Metil 3-(1-etil-3-metil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)propanoato,

5-(4-Clorofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(4-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(4-fluorofenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(3-Bromofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Metil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-(2-Hidroxietil)-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

1-Etil-5-(3-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e]diazepin-8-ona,

5-(2-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(2-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(3-Aminofenil)-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-3-metil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Metil-5-fenil-1-(2,2,2-trifluoroetil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-Ciclohexil-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

261

5-terc-Butil-1-etil-3-metil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

5-(2,4-Dimetoxifenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1h-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

5-(2,4-Dimetoxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazapin-8-ona,

3,5-Di-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3-terc-Butil-5-(2,4-dimetoxifenil)-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-terc-Butil-8-oxo-1-propil-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3-terc-Butil-5-(2,4-dimetoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

1-Etil-3-metil-5-pirid-3-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-pirid-2-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-ilcianamida

N-[4-(1-Etil-3-metil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)fenil]-(fenilsulfonil)bencensulfonamida,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-terc-Butil-1-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Ciclopropilmetil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Alil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-(4-trifluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-(4-trfluorometilfenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-trifluorometilenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3,5-Di-terc-butil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

(±)3-sec-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-5-fenil-1-propil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-etil-5-fenil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-5-fenil-1-propil-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexilmetil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-5-fenil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexilmetil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexilmetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

Etil éster del ácido 1-etil-8-oxo-5-fenil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-3-carboxílico,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-Isopropil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

(±)3-sec-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-(3,4,5-trimetoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(3-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3,5-difenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(4-Hidroxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Etoximetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

9 Un compuesto de acuerdo con las reivindicaciones 1 a 6, elegido del grupo formado por

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-5-(2-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazapin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-Ciclohexil-1-etil-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-metil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

5-(2,4-Dimetoxifenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Isopropil-1-propil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

5-(2,4-Dimetoxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3,5-Di-terc-Butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)-benzonitrilo,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-ilcianamida,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

(±) 3-sec-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±) 3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±) 3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-Isopropil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

(±)3-sec-Butil-1-etil-5-(4-metoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-metil-5-(3,4,5-trimetoxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(3-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3,5-difenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

5-(4-Hidroxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Etoximetil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

271 276

10 Un compuesto de acuerdo con las reivindicaciones 1 a 6, ejegido del grupo formado por

1-Etil-3-metil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-3-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

272

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3,5-Di-terc-butil-1-etil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-terc-Butil-1-etil-8-oxo-1,6,7,8-tetrahidropirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

1-Etil-3-metil-5-fenil-1,6-dihidropirazolo[4,3-e][1,4]diazepin-8-ilcianamida,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

(±)3-sec-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

223 236

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Ciclohexilmetil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-terc-Butil-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-3-isopropil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida,

1-Etil-5-(4-hidroximetil)-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

5-(4-Hidroxifenil)-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

11 Un compuesto de acuerdo con las reivindicaciones 1 a 6, elegido del grupo formado por

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

4-(3-Isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona,

(±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

(±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona,

1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

12 1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

13 3-terc-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

14 1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

15 5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

16 1-Etil-5-(4-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

17 4-(1-Etil-3-isopropil-8-oxo-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

18 5-terc-Butil-3-isopropil-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

19 4-(3-Isopropil-8-oxo-1-propil-1,6,7,8-tetrahidro-pirazolo[4,3-e][1,4]diazepin-5-il)benzonitrilo

20 3-terc-Butil-1-etil-5-p-tolil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

21 3-Butil-1-etil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-tiona

22 (±)3-sec-Butil-1-etil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

23 (±)3-sec-Butil-1-propil-5-pirid-4-il-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

24 3-Ciclohexil-1-propil-5-pirid-4-il-6,7-dihiro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

25 3-terc-Butil-5-(4-metoxifenil)-1-propil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

26 1-Etil-5-(2-hidroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

27 3-terc-Butil-1-etil-5-(4-hidroxifenil)-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

28 1-Etil-3-isopropil-5-fenil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ilidencianamida

29 Una composición farmacéutica caracterizada porque comprende al menos un compuesto definido de acuerdo con cualquiera de las reivindicaciones 1 a 28, en combinación con un soporte farmacéuticamente aceptable

30 Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 28, para su uso como producto farmacéutico

31 Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 28, para su uso como un producto medicinal para tratar enfermedades que incluyen cáncer, síndrome de inmunodeficiencia adquirida fibrosis cicatrices

excesivas que incluyen cicatrices dérmicas excesivas tales como cicatrices dérmicas normales y anormales posteriores a heridas o cirugía, osteoartritis, osteoporosis, esclerosis múltiple, ansiedad, depresión, dermatitis atópica, artritis reumatoidea, ataque séptico, enfermedades inmunes que incluyen lupus eritomatoso diseminado, psoriasis, rechazo de injertos y rinitis alérgica, así como enfermedades que involucran la producción de TNFα, enfermedades inflamatorias tales como asma, bronconeumopatía obstructiva crónica (COPD), lesiones postisquémicas, hipertensión pulmonar, insuficiencia cardíaca congestiva, síndrome de insuficiencia respiratoria aguda, y enfermedades inflamatorias crónicas del intestino (IBD) tales como la enfermedad de Crohn y la colitis ulcertiva

32 Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 28, para su uso como un producto medicinal para tratar enfermedades inflamatorias que comprenden bronconeumopatía obstructiva crónica, asma y enfermedades inflamatorias del intestino (IBD) tales como la enfermedad de Crohn y la colitis ulcerativa

33 Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 28, para su uso como un producto medicinal para tratar enfermedades inflamatorias que comprenden la bronconeumopatía obstructiva crónica, el asma

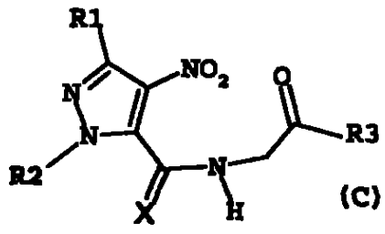
34 Un método para tratar una enfermedad que consiste en un tratamiento con un inhibidor de la fosfodiesterasa 4, el método mencionado caracterizado porque comprende la administración a un paciente de una concentración efectiva de un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 28

35 El uso de un compuesto de la fórmula general I de acuerdo con cualquiera de las reivindicaciones 1 a 28, para preparar un producto medicinal para tratar enfermedades que consiste en una terapia con un inhibidor de la fosfodiesterasa 4

36 Un proceso para preparar un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 28, caracterizado porque comprende los siguientes pasos

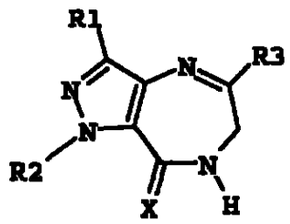
1) cuando, en la fórmula I, X es O o S, W es N y la unión entre W y el átomo de carbono en la posición 5, simbolizada por ═══, es una unión doble

- la ciclización de un compuesto de la fórmula general (C)



(C)

en donde R_1, R_2, R_3 y X tienen el significado dado anteriormente, para dar un intermedio sintético o un compuesto final de la fórmula general D,



(D)

en donde R_1, R_2, R_3 y X tienen los significados dados anteriormente,

2) cuando, en la fórmula I, X es S, W es N y la unión entre W y el átomo de carbono en la posición 5, simbolizada por

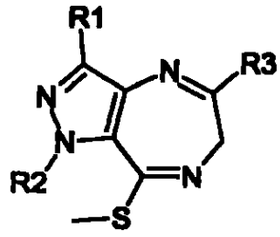
═══, es una union doble

- la tionación de un compuesto de la fórmula general (D), en donde R_1, R_2 y R_3 tienen el significado dado anteriormente y X es O, para dar un compuesto de la fórmula I en donde la unión entre W y el átomo de carbono en la posición 5 es una unión doble, W es N y X es azufre

3) cuando, en la fórmula I, X es N-CN, W es N y la unión entre W y el átomo de carbono en la posición 5, simbolizada por

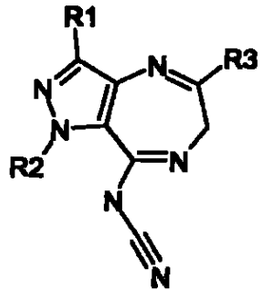
═══, es una unión doble

- la reacción de un compuesto de la fórmula general (G)



(G)

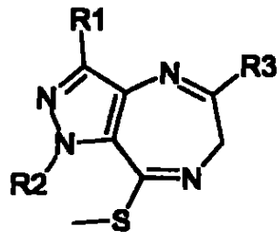
en donde R_1, R_2 y R_3 tienen el significado dado anteriormente, con un compuesto de la fórmula H_2N-CN, para dar un compuesto de la fórmula general F siguiente



(F),

4) cuando, en la fórmula I, X es N-R_8, W es N y la unión entre W y el carbono en la posición 5, simbolizada por ═══, es una unión doble

- la reacción de un compuesto de la fórmula general (G)

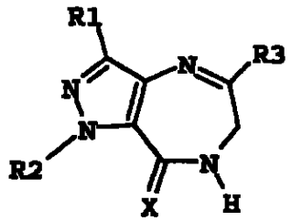


(G)

en donde R_1, R_2 y R_3 son lo definido anteriormente, con un compuesto de la fórmula H_2N-R_B, en donde R_B es lo definido anteriormente, para dar un compuesto de la fórmula I en donde la unión entre W y el átomo de carbono en la posición 5 es una unión doble, W es N y X es $N-R_B$,

5) cuando, en la fórmula I, W es NH y la unión entre W y el átomo de carbono en la posición 5 es una sola unión

- la reacción de un compuesto de la fórmula general (D)

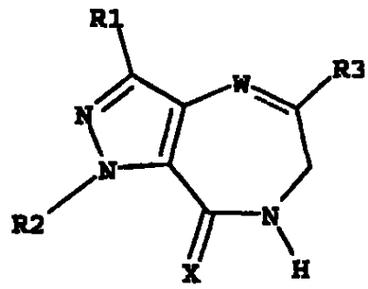


(D)

en donde R_1, R_2, R_3 y X son lo definido anteriormente, con un agente reductor, para dar un compuesto de la fórmula I en donde W es NH y la unión entre W y el átomo de carbono en la posición 5 es una sola unión

RESUMEN DE LA INVENCIÓN

La invención se relaciona con pirazolo[4,3-e]-diazepinas sustituidas novedosas de la fórmula general



I

con composiciones farmacéuticas que las contienen, con su uso como productos medicinales y con procesos para prepararlas

NOVEL SUBSTITUTED PYRAZOLO[4,3-e]DIAZEPINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM, USE AS MEDICINAL PRODUCTS AND PROCESSES FOR PREPARING THEM

The invention relates to novel substituted pyrazolo-[4,3-e]diazepines, to pharmaceutical compositions containing them, to their use as medicinal products and to processes for preparing them

Technological background of the invention

Cyclic adenosine 3',5'-monophosphate (cAMP) is a ubiquitous intracellular second messenger, which is intermediate between a first messenger (hormone, neurotransmitter or autacoid) and the cellular functional responses the first messenger stimulates the enzyme responsible for the synthesis of cAMP, depending on the cells concerned, the cAMP then intervenes in a great number of functions metabolic, contractile or secretory

The effects of cAMP end when it is degraded by cyclic nucleotide phosphodiesterases, which are intracellular enzymes that catalyse its hydrolysis into inactive adenosine 5'-monophosphate

At least 11 major families of cyclic nucleotide phosphodiesterases (PDE) have been distinguished in mammals, numbered from 1 to 11 according to their structure, their kinetic behaviour, their substrate specificity or their sensitivity to effectors (Beavo J A *et al* (1990) Trends Pharmacol Sci 11, 150-155 Beavo J A *et al* (1994) Molecular Pharmacol 46, 399-405) The PDE4 enzymes are specific for cAMP

Non-specific phosphodiesterase inhibitor compounds are known, which inhibit several families of enzymes This is the case for certain methyl xanthines such as theophylline These compounds have a low therapeutic index, in particular on account of their action on types of PDE present in cells other than the target cells Conversely, certain families of PDE can be selectively inhibited by various pharmacological agents the hydrolysis of cyclic nucleotides is slowed down and their concentration thus increases in only the cells in which the type of PDE that is sensitive to the inhibitor is found

A specific advantage is shown for the phosphodiesterases 4 (PDE4), which have been identified in many tissues including the central nervous system, the heart, vascular endothelium, vascular smooth muscle and that of the aerial pathways, myeloid lines and lymphoid lines

An increase in cAMP in the cells involved in inflammation inhibits their activation inhibition of the synthesis and release of mediators in mastocytes, monocytes, polymorphonuclear eosinophils and basophils, inhibition of chemotaxis and degranulation of polymorphonuclear neutrophils and eosinophils, inhibition of the proliferation and differentiation of lymphocytes

Cytokines, in particular TNF and interleukins, produced by various types of leukocytes such as the T lymphocytes, monocytes and polymorphonuclear eosinophils, play an important role in triggering inflammatory manifestations, in particular in response to stimulation by an allergen in the respiratory pathways

Moreover, cAMP reduces the tonus of the smooth muscle fibres in the aerial pathways

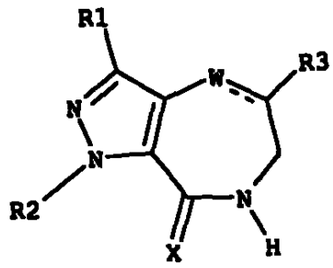
It might thus be expected that selective PDE4 inhibitors would have therapeutic activity as anti-inflammatory and anti-allergic medicinal products, and in the treatment of various respiratory diseases such as asthma, emphysema and chronic bronchitis

Extensive research has been conducted for several years into the production and development of powerful PDE4 inhibitors This is found to be difficult due to the fact that many potential PDE4 inhibitors are not devoid of activity on the phosphodiesterases of other families

At the present time, the lack of selectivity of PDE4 inhibitors thus represents a major problem, given the extent of the functions regulated by cAMP There is thus a need for powerful and selective PDE4 inhibitors, i e inhibitors which have no action with respect to PDEs belonging to other families and particularly PDEs which regulate cGMP

Summary of the invention

The invention relates to substituted pyrazolo[4,3-e]-diazepines of general formula I below



I

in which

R1 is chosen from the following groups

hydrogen,

linear or branched alkyl containing from 1 to 6 carbon atoms,

cycloalkyl containing from 3 to 6 carbon atoms,

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

linear or branched alkenyl containing from 2 to 6 carbon atoms,

the groups $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nC(S)R_B$, $(CH_2)_nC(S)OR_B$, $(CH_2)_nC(S)SR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, $(CH_2)_nNR_DC(O)NR_DR_B$ or $(CH_2)_nZ$, in which,

R_A is chosen from linear or branched alkyl containing from 1 to 6 carbon atoms,

cycloalkyl containing from 3 to 6 carbon atoms,

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur;
arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,
alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,
linear or branched alkenyl containing from 2 to 6 carbon atoms,

R_B and R_C, which may be identical or different, are chosen from hydrogen,
linear or branched alkyl containing from 1 to 6 carbon atoms,
cycloalkyl containing from 3 to 6 carbon atoms,
alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,
aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur;
arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,
alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero

atom chosen from nitrogen, oxygen and sulphur,

linear or branched alkenyl containing from 2 to 6 carbon atoms, it being possible for R_a and R_c to form a ring containing from 5 to 7 atoms which can include one or more hetero atoms chosen from S, N and O,

R_b is hydrogen or linear or branched alkyl containing from 1 to 6 carbon atoms,

Z is a halogen, and

n is an integer from 0 to 4 inclusive,

R2 is chosen from the following groups

linear or branched alkyl containing from 1 to 6 carbon atoms,

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,

cycloalkyl containing from 3 to 6 carbon atoms;

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

linear or branched alkenyl containing from 2 to 6 carbon atoms,

the groups $(CH_2)_mOR_a$, $(CH_2)_nCF_3$, $(CH_2)_mC(O)R_a$, $(CH_2)_mCOOR_a$, $(CH_2)_mOC(O)R_a$, $(CH_2)_mSR_a$, $(CH_2)_mC(S)R_a$, $(CH_2)_mC(S)OR_a$, $(CH_2)_mC(S)SR_a$, $(CH_2)_mNR_bR_c$,

$(CH_2)_mC(O)NR_BR_C$, $(CH_2)_mNR_CC(O)R_B$, $(CH_2)_mNR_DC(O)NR_DR_B$ or $(CH_2)_mZ$, in which,

R_A, R_B, R_C R_D and Z are as defined above, and

m is an integer from 1 to 4 inclusive,

n is an integer from 0 to 4 inclusive,

R3 is chosen from the following groups

hydrogen,

linear or branched alkyl containing from 1 to 6 carbon atoms,

cycloalkyl containing from 3 to 6 carbon atoms,

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur;

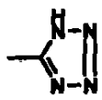
linear or branched alkenyl containing from 2 to 6 carbon atoms,

the groups $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nC(S)R_B$, $(CH_2)_nC(S)OR_B$, $(CH_2)_nC(S)SR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, $(CH_2)_nNR_DC(O)NR_DR_B$ or $(CH_2)_nZ$, in which,

R_A, R_B, R_C R_D and n are as defined above;

the aryl, arylalkyl and alkylaryl groups defined above being unsubstituted or substituted on the aryl group with 1, 2 or 3 groups chosen from

halogen, hydroxyl, NO, NO_2, CN, alkoxy containing from 1 to 4 carbon atoms, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, $(CH_2)_nHNSO_2R_B$, $(CH_2)_nN(SO_2R_B)_2$, CO_2R_B, CF_3 and



in which R_B, R_C and n are as defined above, and

the dotted line present in formula I indicates that the bond between W and the carbon in position 5 may be

- a single bond, in which case W represents a nitrogen atom substituted with a hydrogen atom,
- a double bond, and in this case W represents an unsubstituted nitrogen atom;

X is S, O, N-CN or $N-R_B$ in which R_B is as defined above,

as well as the oxides, the tautomeric forms and the corresponding optical isomers or the pharmaceutically acceptable derivatives of the compounds of formula I,

with the proviso that when

R1 represents a methyl group, R2 an ethyl group, W is N, X is an oxygen atom and the bond between W and the carbon in position 5 is a double bond,

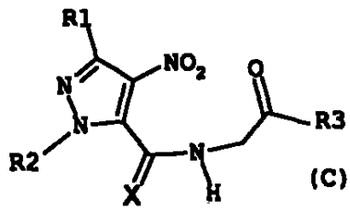
then

R3 is neither an unsubstituted phenyl group nor a phenyl group bearing a fluorine atom in an ortho position as sole substituent

The compounds of the invention have inhibitory properties on PDE4 and/or TNFα-release Some of these compounds are also selective inhibitors of PDE4 subtypes The compounds of the invention can be used in the treatment of complaints including cancer, acquired immunodeficiency syndrome, fibrosis, excessive scarring including excessive dermal scarring such as normal or abnormal dermal scarring following wounding or surgery, osteoarthritis, osteoporosis, multiple sclerosis, anxiety, depression, atopic dermatitis, rheumatoid arthritis, septic shock, immune diseases including disseminated lupus erythematous, psoriasis, graft rejection and allergic rhinitis, as well as diseases involving the production of TNFα and more particularly in the treatment of inflammatory complaints such as asthma, chronic obstructive bronchopneumopathy (COPD), post-ischaemic lesions, pulmonary hypertension, congestive cardiac insufficiency, acute respiratory distress syndrome, and chronic inflammatory diseases of the intestine (IBD) such as Crohn's disease and ulcerative colitis

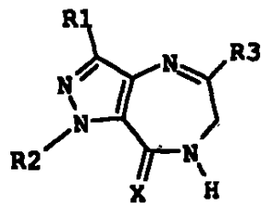
The invention also relates to a process for synthesizing a compound of general formula I, the said process being characterized in that it comprises

1) when, in formula I, X is O or S, W is N and the bond between W and the carbon in position 5, symbolized by ═══ , is a double bond
- the cyclization of a compound of general formula (C)



(C)

in which R1, R2, R3 and X have the meaning given above, to give a synthetic intermediate or a final compound of general formula D,



(D)

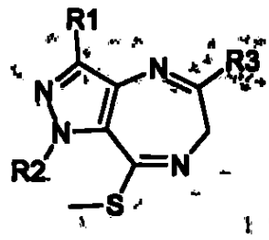
in which R1, R2, R3 and X have the meanings given above,

2) when, in formula I, X is S, W is N and the bond between W and the carbon in position 5, symbolized by ⎓, is a double bond

the thionation of a compound of general formula (D), in which R1, R2 and R3 have the meaning given above and X is O, to give a compound of formula I in which the bond between W and the carbon atom in position 5 is a double bond, W is N and X is sulphur,

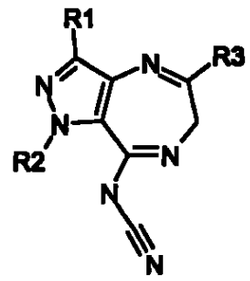
3) when, in formula I, X is N-CN, W is N and the bond between W and the carbon in position 5, symbolized by ⎓, is a double bond

- the reaction of a compound of general formula (G)



(G)

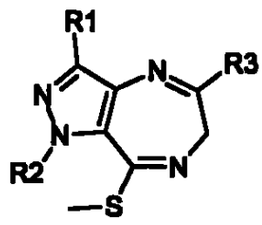
in which R1, R2 and R3 have the meaning given above, with a compound of formula H_2N-CN, to give a compound of geheral formula F below



(F),

4) when, in formula I, X is N-R_8, W is N and the bond between W and the carbon in position 5, symbolized by ---, is a double bond

- the reaction of a compound of general formula (G)



(G)

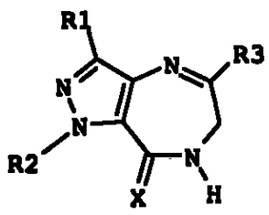
in which R1, R2 and R3 are as defined above, with a compound of formula H_2N-R_8, in which R_8 is as defined above,

to give a compound of formula I in which the bond between W and the carbon atom in position 5 is a double bond, W is N and X is N-R_8 (J Med Chem , 42, 1999, 2909-2919)

295

5) when, in formula I, W is NH and the bond between W and the carbon in position 5 is a single bond

- the reaction of a compound of general formula



(D)

in which R1, R2, R3 and X are as defined above, with a reducing agent, to give a compound of formula I in which W is NH and the bond between W and the carbon in position 5 is a single bond

The invention also relates to a pharmaceutical composition comprising at least one compound of general formula I as defined above, in combination with a pharmaceutically acceptable support

The invention also relates to the use of a substituted pyrazolo[4,*3-e*]diazepine of general formula I as a medicinal product

The invention also relates to the use of a substituted pyrazolo[4,*3-e*]diazepine of general formula I to prepare a medicinal product for treating complaints relating to a therapy with a phosphodiesterase 4 inhibitor

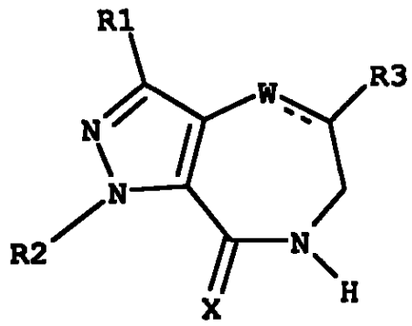
The invention also relates to a method for treating a disease or a complaint relating to a therapy with a phosphodiesterase 4 inhibitor, the said method comprising the administration of an effective concentration of a compound of formula I to a patient

296

The invention also relates to the use of a substituted pyrazolo[4,3-*e*]diazepine of general formula I for the preparation of a medicinal product intended for treating mammals and particularly for treating humans, especially a medicinal product intended for treating conditions including cancer, acquired immunodeficiency syndrome, fibrosis, excessive scarring including excessive dermal scarring such as normal or abnormal dermal scarring following wounding or surgery, osteoarthritis, osteoporosis, multiple sclerosis, anxiety, depression, atopic dermatitis, rheumatoid arthritis, septic shock, immune diseases including disseminated lupus erythematous, psoriasis, graft rejection, allergic rhinitis, diseases involving the production of TNFα and more particularly inflammatory complaints such as asthma, chronic obstructive bronchopneumopathy (COPD), post-ischaemic lesions, pulmonary hypertension, congestive cardiac insufficiency, acute respiratory distress syndrome, and chronic inflammatory diseases of the intestine (IBD) such as Crohn's disease and ulcerative colitis

Detailed description of the invention

The present invention thus relates to the compounds of general formula I

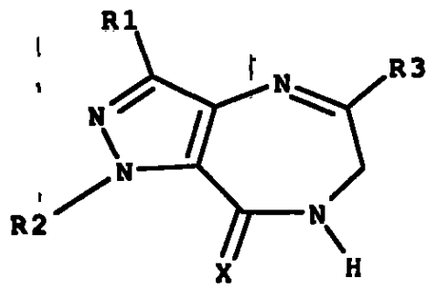


I

in which the dotted line, X, W, R1, R2 and R3 are as defined above

The compounds of formula I above in which W represents an unsubstituted nitrogen atom and the bond between W and the carbon in position 5, symbolized by ---, is a double bond, are preferred

Among the compounds of general formula I that are thus preferred are the compounds corresponding to the general formula II



II

in which

R1 is a linear or branched alkyl group containing from 1 to 6 carbon atoms;

a cycloalkyl group containing from 3 to 6 carbon atoms,

an alkylcycloalkyl group comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

an aryl group containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

an arylalkyl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

an alkylaryl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

a linear or branched alkenyl group containing from 2 to 6 carbon atoms,

the groups $(CH_2)_nOR_a$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_a$, $(CH_2)_nCOOR_a$, $(CH_2)_nOC(O)R_a$, $(CH_2)_nSR_a$, $(CH_2)_nNR_aR_c$, $(CH_2)_nC(O)NR_aR_c$, $(CH_2)_nNR_cC(O)R_a$ or $(CH_2)_nZ$, in which

R_a is chosen from linear or branched alkyl containing from 1 to 6 carbon atoms,

cycloalkyl containing from 3 to 6 carbon atoms,

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero

atom chosen from nitrogen, oxygen and sulphur,
alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,
linear or branched alkenyl containing from 2 to 6 carbon atoms,

R_B and R_C, which may be identical or different, are chosen from hydrogen;
linear or branched alkyl containing from 1 to 6 carbon atoms,
cycloalkyl containing from 3 to 6 carbon atoms,
alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,
aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,
arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur
alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur
linear or branched alkenyl containing from 2 to 6 carbon atoms,

R_B and R_C possibly forming a ring containing from 5 to 7 atoms which may include one or more hetero atoms chosen from S, N or O,

Z is a halogen, and

n is an integer from 0 to 4 inclusive;

R2 is a linear or branched alkyl group containing from 1 to 4 carbon atoms,

$(CH_2)_nCF_3$, in which n is an integer from 0 to 4 inclusive,

methylcyclopropyl,

linear or branched alkenyl containing from 2 to 6 carbon atoms,

or a group $(CH_2)_mOR_B$ and $(CH_2)_mCO_2R_B$, in which m is an integer from 1 to 3 inclusive and R_B is as described above,

R3 is a linear or branched alkyl group containing from 1 to 6 carbon atoms,

a cycloalkyle group containing from 3 to 6 carbon atoms,

an alkylcycloalkyl group comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,

an aryl group containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

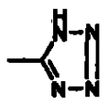
an arylalkyl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

an alkylaryl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,
an linear or branched alkenyl group containing from 2 to 6 carbon atoms,
the groups $(CH_2)_nOR_B$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$ and $(CH_2)_nNR_CC(O)R_B$, in which,

R_A, R_B, R_C and n are as defined above,

the aryl, arylalkyl and alkylaryl groups defined above being unsubstituted or substituted on the aryl group with 1, 2 or 3 groups chosen from

halogen, hydroxyl, NO, NO_2, CN, alkoxy containing from 1 to 4 carbon atoms, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$ $(CH_2)_nNC(O)R_B$, $(CH_2)_nHNSO_2R_B$, $(CH_2)_nN(SO_2R_B)_2$, CO_2R_B, CF_3 and



in which R_B, R_C and n are as defined above, and,

X is O, S or NCN

The invention relates particularly to the compounds of general formula II in which

R1 is a linear or branched alkyl group containing from 1 to 6 carbon atoms,
a cycloalkyl group containing from 3 to 6 carbon atoms,
an alkylcycloalkyl group comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,

an aryl group containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

an alkylaryl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur;

a linear or branched alkenyl group containing from 2 to 6 carbon atoms,

the groups $(CH_2)_nOR_B$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$ or $(CH_2)_nZ$, in which,

R_A is chosen from linear or branched alkyl containing from 1 to 6 carbon atoms,

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

R_B and R_C, which may be identical or different, are chosen from hydrogen,

linear or branched alkyl containing from 1 to 6 carbon atoms,

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

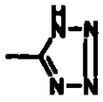
n is an integer from 0 to 4 inclusive;

R2 is a linear or branched alkyl group containing from 1 to 4 carbon atoms or a group $(CH_2)_mOH$ or $(CH_2)_mCO_2H$, in which m is an integer from 1 to 3 inclusive,

R3 is a linear or branched alkyl group containing from 1 to 6 carbon atoms
a cycloalkyl group containing from 3 to 6 carbon atoms,
an aryl group containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,
an arylalkyl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,
an alkylaryl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

the aryl, arylalkyl and alkylaryl groups defined above being unsubstituted or substituted on the aryl group with 1, 2 or 3 groups chosen from

halogen, hydroxyl, NO, NO_2, CN, alkoxy containing from 1 to 4 carbon atoms, $(CH_2)_nOR_a$, $(CH_2)_nNR_aR_c$ $(CH_2)_nNC(O)R_a$, CO_2R_a, CF_3 and



in which R_a, R_c and n are as defined above, and

X is O, S or NCN

The invention relates more particularly to the compounds of general formula II in which

R1 is a linear or branched alkyl group containing from 1 to 4 carbon atoms,
a cycloalkyl group containing from 3 to 6 carbon atoms,
an alkylcycloalkyl group comprising an alkyl group containing from 1 to 3 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,

R2 is a linear or branched alkyl group containing from 1 to 4 carbon atoms,

R3 is a linear or branched alkyl group containing from 1 to 4 carbon atoms,
an aryl group containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur, preferably phenyl or pyridyl, the aryl groups being unsubstituted or substituted with 1, 2 or 3 groups, which may be identical or different, chosen from NH_2, halogen, methoxy, hydroxyl, CN, CH_3 and CF_3, and,

X is O, S or NCN

The invention also preferably relates to compounds of general formula II in which

R1 is a linear or branched alkyl group containing from 1 to 4 carbon atoms,

R2 is a linear or branched alkyl group containing from 1 to 4 carbon atoms or a group $(CH_2)_nOH$, in which n is an integer from 1 to 4 inclusive;

R3 is a linear or branched alkyl group containing from 1 to 4 carbon atoms, a cycloalkyl group containing from 3 to 6 carbon atoms, an aryl group chosen from phenyl and thienyl, which may be unsubstituted or substituted with a group chosen from halogen, hydroxyl, methoxy, NH_2 and CH_3; and

X is S or O

The invention also preferably relates to the compounds of general formula I in which

R1 is a linear or branched alkyl group containing from 1 to 4 carbon atoms,

R2 is a linear or branched alkyl group containing from 1 to 4 carbon atoms or a group $(CH_2)_nOH$, in which n is an integer from 1 to 4 inclusive;

R3 is a linear or branched alkyl group containing from 1 to 4 carbon atoms, a cycloalkyl group containing from 3 to 6 carbon atoms, an aryl group chosen from phenyl and thienyl, which may be unsubstituted or substitued with a group chosen from halogen, hydroxyl, methoxy, NH_2, CH_3, and

X is S

Among the groups defined above, the following substituents are particularly preferred

The linear or branched alkyl group contains from 1 to 6 carbon atoms and preferably from 1 to 4 carbon atoms Examples of such groups are, inter alia, methyl, ethyl, n-propyl and isopropyl, tert-butyl, n-butyl, sec-butyl and isobutyl

The linear or branched alkenyl group contains from 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms Examples comprise ethylidene, propylidene and butylidene

The alkylcycloalkyl group comprises a linear or branched alkyl group containing from 1 to 6 carbon atoms, particularly from 1 to 4 carbon atoms, and a cycloalkyl group containing from 3 to 6 carbon atoms Examples include methylcyclopropyl, methylcyclobutyl and methylcyclohexyl

The cycloalkyl group comprises from 3 to 6 carbon atoms Examples are cyclopropyl, cyclopentyl and cyclohexyl.

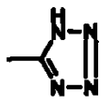
The aryl group is an aromatic group containing from 5 to 10 carbon atoms Examples of such groups are phenyl, benzyl, tolyl and naphthyl This aryl group can optionally be interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur The term "interrupted" means that the hetero atom can replace a carbon atom of the ring Examples of such groups containing a hetero atom are, inter alia, thienyl and pyridyl

The term alkylaryl corresponds to a group containing an alkyl group and an aryl group as defined above, linked to the rest of the molecule via the alkyl group

The term arylalkyl corresponds to a group containing an alkyl group and an aryl group as defined above, linked to the rest of the molecule via the aryl group

The aryl, alkylaryl and arylalkyl groups defined above can be unsubstituted or substituted on the aryl group with 1, 2 or 3 groups chosen from

halogen, hydroxyl, NO, NO_2, alkoxy containing from 1 to 4 carbon atoms, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, $(CH_2)_nOR_B$, $(CH_2)_nHNSO_2R_B$, CO_2R_B, CF_3 and



in which R_B, R_C and n are as defined above

Halogen comprises chlorine, bromine, fluorine and iodine

The compounds listed below are among the preferred compounds of the present invention

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1,3-Dimethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Methoxyphenyl)-1,3-dimethyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

5-(4-Bromophenyl)-1,3-dimethyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-naphth-2-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(3-Chlorothien-2-yl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
Methyl 3-(1-ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-e][1,4]diazepin-5-yl)propanoate ,
1-Ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Chlorophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-5-(4-fluorophenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(3-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Isopropyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
(±)1-Ethyl-3-methyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-(2-Hydroxyethyl)-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione,
1-Ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

1-Ethyl-5-(3-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(2-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(2-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one, isomer 1,
1-Ethyl-3-methyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one, isomer 2,
3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-methyl-5-p-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(3-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1H-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-(4-Aminophenyl)-3-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Aminophenyl)-3-methyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Methyl-5-phenyl-1-(2,2,2-trifluoroethyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1,5-Diethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-Cyclohexyl-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
(±)1-Ethyl-3-methyl-5-pyrid-4-yl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-*tert*-Butyl-1-ethyl-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Diethylaminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
N-[4-(1-Ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)phenyl]acetamide,
4-(1-Ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
1-Ethyl-3-isopropyl-5-(4-pyrrolidin-1-yl-phenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(2,4-Dimethoxyphenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-Isopropyl-8-oxo-1-propyl-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
3-Isopropyl-1-propyl-5-(4-pyrrolidin-1-yl-phenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(2,4-Dimethoxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3,5-Di-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-*tert*-Butyl-1-ethyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
3-*tert*-Butyl-1-ethyl-5-(4-pyrrolidin-1-yl-phenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3,5-Di-*tert*-butyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-*tert*-Butyl-8-oxo-1-propyl-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
3-tert-Butyl-1-propyl-5-(4-pyrrolidin-1-yl-phenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-methyl-5-pyrid-3-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-methyl-5-pyrid-2-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-phenyl-1,6-dihydropyrazolo[4,3-*e*][1,4]diazepin-8-ylcyanamide,
N-[4-(1-Ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)phenyl]-(phenylsulphonyl)benzenesulphonamide,
(1-Ethyl-3-methyl-5-phenyl-1,6-dihydropyrazolo[4,3-*e*][1,4]diazepin-8-yl)methylamine,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
3-tert-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
1-Cyclopentyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Cyclopropylmethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Cyclobutylmethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Allyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-tert-Butyl-1-ethyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
3,5-Di-tert-butyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-tert-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-5-phenyl-1-propyl-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexyl-1-ethyl-5-phenyl-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexyl-5-phenyl-1-propyl-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexylmethyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexylmethyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexylmethyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexylmethyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-8-oxo-5-phenyl-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-3-carboxylic acid ethyl ester,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
1-Ethyl-3-isopropyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
3-Isopropyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
(±)3-*sec*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-(3,4,5-trimethoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(3-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-(2,3,4-trimethoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3,5-diphenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-(4-Hydroxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-tert-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(2,6-Dimethoxyphenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-Ethoxymethyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

Among the preferred compounds defined above, the following compounds are preferred

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-naphth-2-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(3-Chlorothien-2-yl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
Methyl 3-(1-ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4,3-e][1,4]diazepin-5-yl)propanoate,
5-(4-Chlorophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-5-(4-fluorophenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(3-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

1-(2-Hydroxyethyl)-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione,
1-Ethyl-5-(3-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(2-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-5-(2-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-yrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-p-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(3-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-thione,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione,
5-(4-Aminophenyl)-3-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Aminophenyl)-3-methyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-Methyl-5-phenyl-1-(2,2,2-trifluoroethyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

5-Cyclohexyl-1-ethyl-3-methyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

1-Ethyl-3-methyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-*tert*-Butyl-1-ethyl-3-methyl-4 5 6 7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

3-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one

5-*tert*-Butyl-1-ethyl-3-isopropyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4 3-*e*][1,4]diazepin-5-yl)benzonitrile,

5-(2,4-Dimethoxyphenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

4-(3-Isopropyl-8-oxo-1-propyl-1 6 7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

5-(2,4-Dimethoxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

3,5-Di-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

4-(3-*tert*-Butyl-1-ethyl-8-oxo-1,6 7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one

318

3 5-Di-*tert*-butyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one,

4-(3-*tert*-Butyl-8-oxo-1-propyl-1,6,7,8-tetrahydro-pyrazolo[4 3-*e*][1 4]diazepin-5-yl)benzonitrile

3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-propyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

3-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-thione,

1-Ethyl-3-methyl-5-pyrid-3-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

1-Ethyl-3-methyl-5-pyrid-2-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-methyl-5-phenyl-1,6-dihydropyrazolo[4,3-*e*][1,4]diazepin-8-ylcyanamide,

N-[4-(1-Ethyl-3-methyl-8-oxo-1 6 7,8-tetrahydro-pyrazolo[4,3-*e*][1 4]diazepin-5-yl)phenyl]-(phenylsulphonyl)benzenesulphonamide

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-ylidenecyanamide

3-*tert*-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-ylidenecyanamide,

1-Cyclopropylmethyl-3-methyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

1-Allyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

1-Ethyl-3-methyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-isopropyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione

3 5-Di-*tert*-butyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

5-*tert*-Butyl-3-isopropyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-thione

(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

(±)3-*sec*-Butyl-5-phenyl-1-propyl-4-yl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

3-Cyclohexyl-1-ethyl-5-phenyl-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

3-Cyclohexyl-5-phenyl-1-propyl-4-yl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one

3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

3-Cyclohexylmethyl-1-ethyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

3-Cyclohexylmethyl-5-phenyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

3-Cyclohexylmethyl-1-propyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

3-Cyclohexylmethyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-one

1-Ethyl-8-oxo-5-phenyl-1,6 7,8-tetrahydropyrazolo[4,3-e][1,4]diazepin-3-carboxylic acid ethyl ester,

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-ylidenecyanamide,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-ylidenecyanamide

1-Ethyl-3-isopropyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4 3-e][1 4]diazepin-8-one,

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-thione

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-ylidenecyanamide

3-Isopropyl-5-(4-methoxyphenyl)-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

3-*tert*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-one

1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-ylidenecyanamide,

(±)3-*sec*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(±)3-*sec*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-one,

1-Ethyl-3-methyl-5-(3 4 5-trimethoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4 3-e][1 4]diazepin-8-one

1-Ethyl-5-(3-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

1-Ethyl-3 5-diphenyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one,
5-(4-Hydroxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one
3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one
3-Ethoxymethyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

Among the preferred compounds defined above, the following compounds are preferred

1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-thione
1-Ethyl-5-(2-methoxyphenyl)-3-methyl-6 7-dihydro-1*H*-yrazolo[4,3-*e*][1 4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one
3-*tert*-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-tert-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1H-pyrazolo[4,3-e][1 4]diazepin-8-thione,
1-Ethyl-3-isopropyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione
5-(4-Aminophenyl)-3-*tert*-butyl-1-ethyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one,
5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one

5-Cyclohexyl-1-ethyl-3-methyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

1-Ethyl-3-methyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

5-*tert*-Butyl-1-ethyl-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

3-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4 3-*e*][1,4]diazepin-5-yl)benzonitrile,

5-(2 4-Dimethoxyphenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Isopropyl-1-propyl-5-*p*-tolyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

4-(3-Isopropyl-8-oxo-1-propyl-1 6 7 8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

5-(2,4-Dimethoxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

3,5-Di-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

4-(3-*tert*-Butyl-1-ethyl-8-oxo-1 6 7 8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

3-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-thione

323

1-Ethyl-3-methyl-5-phenyl-1 6-dihydropyrazolo[4,3-e][1 4]diazepin-8-ylcyanamide

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1 4]diazepin-8-ylidenecyanamide,

3-*tert*-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4 3-e][1 4]diazepin-8-ylidenecyanamide

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-thione

(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one

(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one,

3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-one,

3-Cyclohexylmethyl-1-ethyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-ylidenecyanamide,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1 4]diazepin-8-ylidenecyanamide

1-Ethyl-3-isopropyl-5-(4-methoxyphenyl)-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-ylidenecyanamide,

3-Isopropyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1 4]diazepin-8-one

3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1 4]diazepin-8-one

1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-ylidenecyanamide

(±)3-*sec*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

1-Ethyl-3-methyl-5-(3,4 5-trimethoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

1-Ethyl-5-(3-hydroxyphenyl)-3-methyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

1-Ethyl-3 5-diphenyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

1-Ethyl-5-(4-hydroxyphenyl)-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

5-(4-Hydroxyphenyl)-3-isopropyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

3-Ethoxymethyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one

Among the preferred compounds defined above the following compounds are preferred

1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-thione

1-Ethyl-3-isopropyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

3-tert-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-tert-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1H-pyrazolo[4,3-*e*][1,4]diazepin-8-thione

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-thione

5-(4-Aminophenyl)-3-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

5-*tert*-Butyl-1-ethyl-3-isopropyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one

4-(1-Ethyl-3-isopropyl-8-oxo-1 6 7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

4-(3-Isopropyl-8-oxo-1-propyl-1,6,7,8-tetrahydropyrazolo[4 3-*e*][1,4]diazepin-5-yl)benzonitrile,

3 5-Di-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

4-(3-tert-Butyl-1-ethyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4 3-*e*][1,4]diazepin-5-yl)benzonitrile,

3-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-thione,

1-Ethyl-3-methyl-5-phenyl-1 6-dihydropyrazolo[4 3-*e*][1,4]diazepin-8-ylcyanamide,

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide

3-*tert*-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-ylidenecyanamide

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione

(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one,

3-Cyclohexylmethyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-ylidenecyanamide

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-ylidenecyanamide,

1-Ethyl-5-(4-hydroxyphenyl)-3-isopropyl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

5-(4-Hydroxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one

3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

Among the preferred compounds of the present invention the compounds below are particularly preferred

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-isopropyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-thione

5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile

5-*tert*-Butyl-3-isopropyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

4-(3-Isopropyl-8-oxo-1-propyl-1 6 7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-thione,

(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,

1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-ylidenecyanamide

Derivatives of the compounds of the invention

The compounds used in the invention include the solvates, the hydrates the pharmaceutically acceptable salts and the polymorphs (different crystal structures) of the compounds according to the invention, which are designated as being pharmaceutically acceptable derivatives thereof

The pharmaceutically acceptable salts include, for example acetate, benzenesulphonate benzoate, bicarbonate, bitartrate, bromide calcium acetate, camsylate carbonate, chloride, citrate dihydrochloride edetate, edisylate, estolate, esylate, fumarate gluceptate, gluconate, glutamate, glycoloylarsanilate hexylresorcinate hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide isethionate lactate lactobionate, malate, maleate mandelate mesylate, methyl bromide methyl nitrate, methyl sulphate mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate polygalacturonate, salicylate, stearate, subacetate, succinate sulphate, tannate, tartrate, theoclate triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine meglumine procaine aluminium, calcium lithium, magnesium, potassium, sodium and zinc (see also Pharmaceutical salts by Berge S M *et al* (1997) J Pharm Sci **66** 1-19 the content of which is incorporated into the present invention by way of reference)

The use of a prodrug of a compound according to the invention is also envisaged (See in particular Bundgaard, *et al* , Acta Pharm Suec 1987 **24** 233-246)

Mixtures of compounds are also envisaged

Pharmaceutical formulation of the compounds of the invention

The compounds of the invention are administered in the form of compositions that are appropriate for the nature and seriousness of the complaint to be treated The daily dosage in man is usually between 2 mg and 1 g of product which can be absorbed in one or more intakes The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0 5 to 60% by weight of active principle (compound of formula I) and 40 to 99 5% by weight of pharmaceutically acceptable vehicle The compositions of the present invention are thus prepared in forms that are compatible with the desired route of administration By way of example the following pharmaceutical forms may be envisaged although the list given below is not limiting

1) Forms for oral administration

Tablets, cachets, sachets of powder for drinkable suspension, gel capsules, gastro-resistant gel capsules, sustained-release forms, emulsions, HPMR wafer capsules or gel capsules, lyophilizates to be melted under the tongue, drinkable solutions, suspensions and sachets of powder for a drinkable solution

The powders tablets, cachets or encapsulated forms preferably contain from 5% to 70% of active principle Suitable supports are, for example, magnesium carbonate, magnesium stearate, talc, lactose sugar, pectin, dextrin, starch, gum tragacanth methylcellulose sodium carboxymethylcellulose, low-melting wax, cocoa butter and the like

The tablets powders cachets and capsules can be used as a unit dosage for oral administration

In the powders, the support is a finely divided solid which is in a mixture with the finely divided compound of general formula I

In the tablets the active compound is mixed with the support which has the required binding properties, in a suitable amount and the mixture is then tableted into the required shape and size

The aqueous solutions for oral administration can be prepared by dissolving the active principle and adding, if necessary, dyes, flavour enhancers, flavourings, stabilizers thickeners etc By way of example the active principle can be dispersed in the form of finely divided powder in water with a viscous material such as synthetic gums, resins methylcellulose sodium carboxymethylcellulose and other suspension agents known in the pharmaceutical field

2) Forms for parenteral administration

Intravenous route

Aqueous solutions, water/co-solvent solutions, solutions using one or more solubilizing agents, colloidal suspensions emulsions nanoparticulate suspensions which can be used for injecting sustained-release forms, dispersed forms and liposomes

Sterile solutions of the active principle in water and/or propylene glycol can be mentioned as examples of liquid preparations which are suitable for parenteral

administration The liquid preparations can also be formulated in the form of aqueous solutions of polyethylene glycol

Subcutaneous/intramuscular route

In addition to the forms that can be used intravenously which can also be used for the subcutaneous and intramuscular routes, other types of forms such as suspensions, dispersed forms, sustained-release gels and sustained-release implants can also be used

3) Forms for topical administration

Among the most common topical forms are creams, gels (aqueous phases gelled with polymers) patches, which are dressings to be stuck directly on the skin and which can be used for treating dermatoses without percutaneous penetration of the active substance sprays emulsions and solutions

4) Forms for pulmonary administration

Distinguished in this category are forms such as solutions for aerosols powders for inhalers and other suitable forms

5) Forms for nasal administration

This relates especially to solutions or suspension for drops

6) Forms for rectal administration

Suppositories and gels will be selected, inter alia

For the preparation of suppositories, a low-melting wax, such as a mixture of fatty acid glycerides and cocoa

butter, is melted in a first stage, and the active principle is then dispersed therein, for example with mechanical stirring The molten homogeneous mixture is then poured into moulds of appropriate shape and then left to cool and solidify

It may also be envisaged to use forms allowing the administration of ophthalmic solutions or allowing the administration of the active principle via the vaginal route

Another important category of pharmaceutical form which can be used in the context of the present invention relates to forms for improving the solubility of the active principle By way of example, it may be envisaged to use aqueous solutions of cyclodextrin and more particularly forms comprising hydroxypropyl beta cyclodextrin A detailed review of this type of pharmaceutical form is given in the article published under the reference *Journal of Pharmaceutical Sciences 1142-1169, 85 (11), 1996,* and incorporated into the present patent application by way of reference

The various pharmaceutical forms recommended above are described in detail in the book « Pharmacie galenique [Pharmaceutical pharmacy]» by A Lehir *(published by Masson, 1992 (6th edition))*, which is incorporated into the present patent application by way of reference

Synthesis of the compounds of the present invention

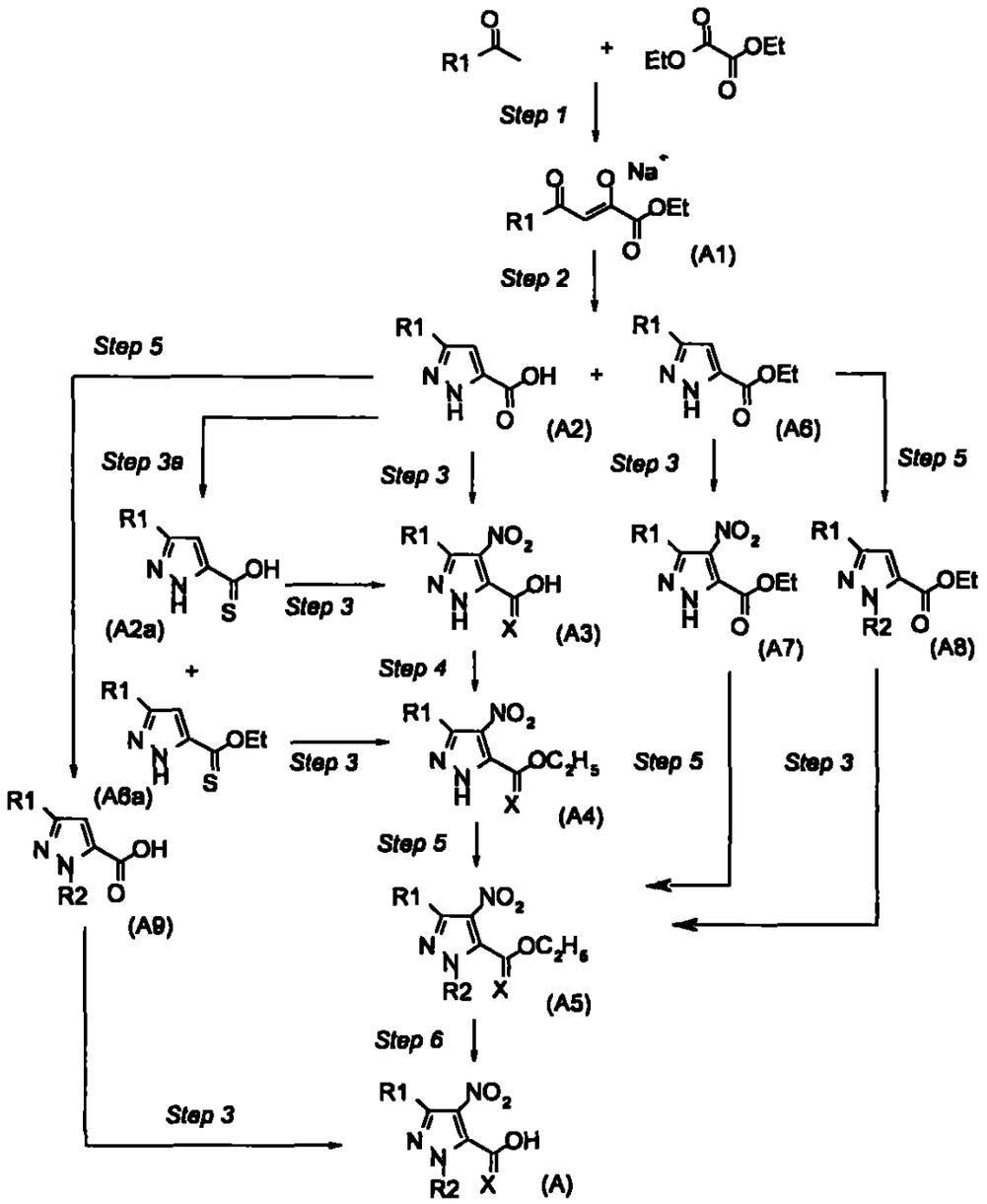
A subject of the invention is also a process for preparing the compounds according to the invention, as illustrated in the reaction schemes below The starting materials are

commercially available or can be synthesized by standard methods

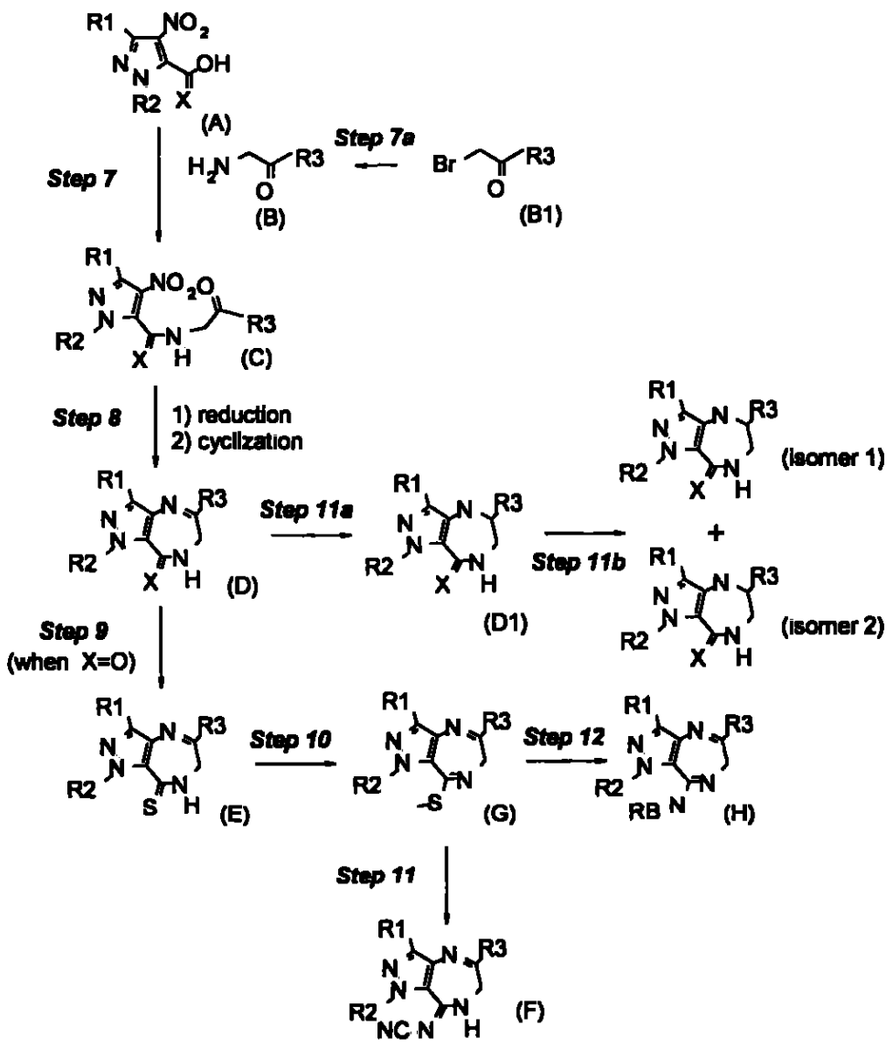
Reaction scheme 1

In the description which follows, each of the steps of the reaction scheme is described in general This process and its various steps are exemplified in Example 1 If a step can be carried out according to various methods (depending on the compounds under consideration), they will be described (M1, M2) and identified relative to a literature reference The starting materials are chosen in an appropriate manner (it being possible for the reactive functions, if any, to be protected in a conventional manner)

Reaction scheme 1



Reaction scheme 1 (continued)



Step 1

An R1-methyl ketone in which R1 is one of the substituents of the compound of general formula I is reacted with a diethyl oxalate in the presence of sodium to give the compound of general formula A1

Step 2

A cyclization of the compound A1 is then carried out, for example with hydrazine sulphate in the presence of potassium hydroxide to give a mixture of the pyrazole (A2) and the pyrazole (A6) each comprising the substituent R1 These two intermediates may be separated and reacted subsequently

Step 3a

Step 3a is an alternative step to step 9 described below It allows the introduction of a sulphur atom into the position of the substituent X from the very first steps of the synthesis by reacting A2 or A6 with a suitable reagent for example Lawesson's reagent, to give a compound of formula A2a or A6a in which X is equal to O or S and R1 is defined as above

Step 3

Step 3 essentially comprises the nitration of the pyrazole nucleus This nitration is carried out on the compounds A2, A2a, A6, A6a, A8 or A9 and can be carried out according to 3 methods desribed in the literature

- using $NaNO_3/H_2SO_4$ (method M1) see Example 1 *Aust J Chem* , 47, 1009-1021, 1994
- using $HNO_3/H\ SO_4$, (method M2)
- or using $Cu(NO_3)_2$ (method M3), *J Org Chem* 46, 3056-3060 1981

to give a compound of formula A A3, A4 A5 or A7 in which X is equal to O or S

Step 4

In this step compound A3 is esterified This can be carried out by reacting compound A3 with ethanol in acidic medium Compound A4 in which X is equal to O or S and R1 is as defined above is thus obtained

Step 5

The pyrazoles A2, A4, A6 and A7 are alkylated according to various methods

- by reacting dimethyl sulphate (to give derivatives with R2 = ethyl)(methode M4), *J Med Chem* 16, 12, 1346-1354, 1973

- by reacting with a compound of the type R2-hal, in which R2 is as defined for the compound of general formula I and hal is a halogen (method M5)

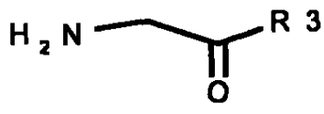
A compound of formula A5, A8 or A9 in which X is equal to O or S is obtained

Step 6

During this step the ester function (X = O) or thioester function (X = S) is hydrolysed for example by reacting compound A5 with sodium hydroxide This gives compound A in which X is equal to O or S and R1 and R2 are as defined above

Step 7

During this step, compound A is reacted with compound B of general formula



in which R3 is one of the substituents of the compound of general formula I Preferably a hydrochloride of compound B is used When it is not commercially available the product (B) is synthesized in one step (step 7a), starting with compound (B1), which is commercially available or described in the literature The nucleophilic substitution of the bromine with the primary amine function is obtained according to various methods

Delepine method (method M6), *J Heterocyclic Chem* , 24, 297-301, 1987

Method via the synthesis of a bisformamide (method M7) *Tetrahedron Lett* 30, 39, 5285-58-286 1889 *Synthesis*, 122-124 1990

Compound C in which X is equal to O or S is obtained according to various coupling methods (step 7)

Method of coupling N-hydroxysuccinimide and dicyclohexylcarbodiimide (method M8, see example 1)

Method of coupling on a solid support (method M9) compound A (1 eq) is reacted with N-cyclohexylcarbodiimide and N -methylpolystyrene HL (2 eq) in dichloromethane After stirring for half an hour compound B (1 eq) and triethylamine (1 eq) are added After 24 hours at room temperature, methyl isocyanate polystyrene HL is added After 2 hours, the reaction medium is filtered and the filtrate is concentrated to give compound C in which X is equal to O or S

Method of coupling with EDCI 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride and HOBt (1-hydroxybenzotriazole) (method M10) compound B is reacted, with stirring with compound A in equimolar amount in dichloromethane in the presence of one

equivalent of triethylamine one equivalent of 1-hydroxybenzotriazole and one equivalent of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride After 24 hours at room temperature, the reaction medium is washed with water the organic phase is dried and evaporated to dryness to give the compound of formula C in which X is equal to O or S and R1 R2 and R3 are as defined above

Step 8

During this step, compound C is cyclized according to various methods to give compound D in which X is equal to O or S and R1, R2 and R3 are as defined above

using Fe/HCl (method M11) (see example 1)

using $SnCl_2$ (method M12) an amide of type C is dissolved in ethanol with 5 equivalents of tin chloride dihydrate The reaction medium is refluxed for 4 hours After cooling to room temperature, demineralized water is added and, when cold, the solution is brought to basic pH with 30% sodium hydroxide After extraction with CH_2Cl_2 and drying the medium is evaporated to dryness to give the compound of type D, which is purified, if necessary on silica or by crystallization

Step 9

Step 9 is used when it is desired to obtain a compound of formula I in which X is S if, in compound D, X is O The compounds of this type are obtained by reacting compound D, in which X is O, with a suitable reagent, allowing its thionation to be carried out By way of example, Lawesson's reagent may be used A compound of formula E in which X is S is thus obtained

Steps 10 and 11

Steps 10 and 11 are used when it is desired to obtain a compound of formula I in which X is N-CN The compounds of this type are obtained according to various methods

method M13 by reacting compound E with sodium hydride and then with iodomethane to give compound (G) This compound is then placed in contact with cyanamide and triethylamine to give a compound of type (F) *Heterocycles*, **36** 777-783, 1993

method M14 $Ph_3PSnN=C=NSnPPh_3$ in ethanol *J Med Chem* , **35**, 12, 2327-2340 1992

method M15 phosphoryl chloride, cyanamide and triethylamine *Chem Pharm Bull* , **42**, 12, 2475-2482, 1994

method M16 cyanamide triethylamide [sic] mercury acetate and acetonitrile *Can J Chem* , **63**, 3089-3101 1985

Steps 11a and 11b

Step 11a makes it possible to reduce the imine function of compound D by reacting it with a reducing agent, for example $NaBH_4$ in a polar mixture for example methanol/water in the presence of palladium-on-charcoal to give the racemate D1 in which X is O or S and R1, R2 and R3 are as defined above, and the following step (11b) corresponds to the separation of the enantiomers (isomer 1 and isomer 2), for example by means of HPLC on a Diacel OD-H chiral column (250 mm × 4 6 mm 5 µm, flow rate 1 ml/min 80/20 heptane/isopropanol)

These steps, 11a and 11b, also apply in the case of a compound of formula D in which X is N-CN or $N-R_8$

347

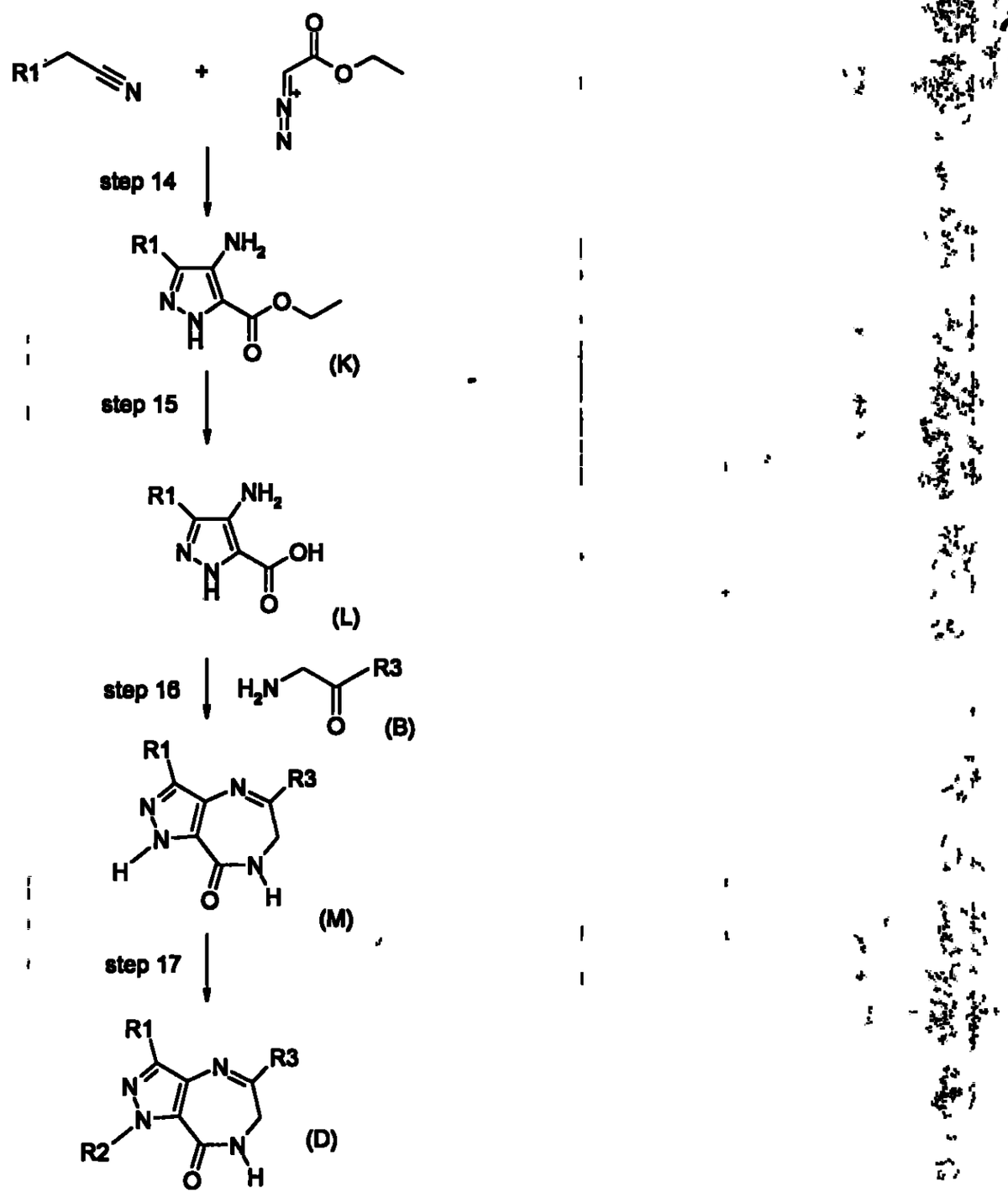
Steps 10 and 12

Steps 10 and 12 are used to obtain compounds of the type H Step 10 allows the formation of the derivative G and step 12 leads to the introduction of the group N-RB according to a method inspired by the literature *J Med Chem* **42** 2909-2919, 1999

Reaction scheme 2

This reaction scheme results in the synthesis of derivatives D in which X is O with R1 = aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur and R2 and R3 are as defined above This process is illustrated by Example 4

Reaction scheme 2



Step 14

The synthesis of the pyrazole is carried out under the conditions described in *Farmaco Ed Sci* , 39, 7, 1984, 618-636

Step 15

During this step, the ester function of compound K is hydrolysed, for example by reacting compound K with sodium hydroxide This gives compound L

Step 16

This step leads to the formation of the derivative M after coupling with compound B and cyclization

Step 17

This step allows the formation of the compounds D with X = O and R1 = aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur and R2 and R3 are as defined above

Compound M is alkylated by reacting it with a compound of the type R2-hal, in which R2 is as defined for the compound of general formula I and hal is a halogen Compound D is thus obtained

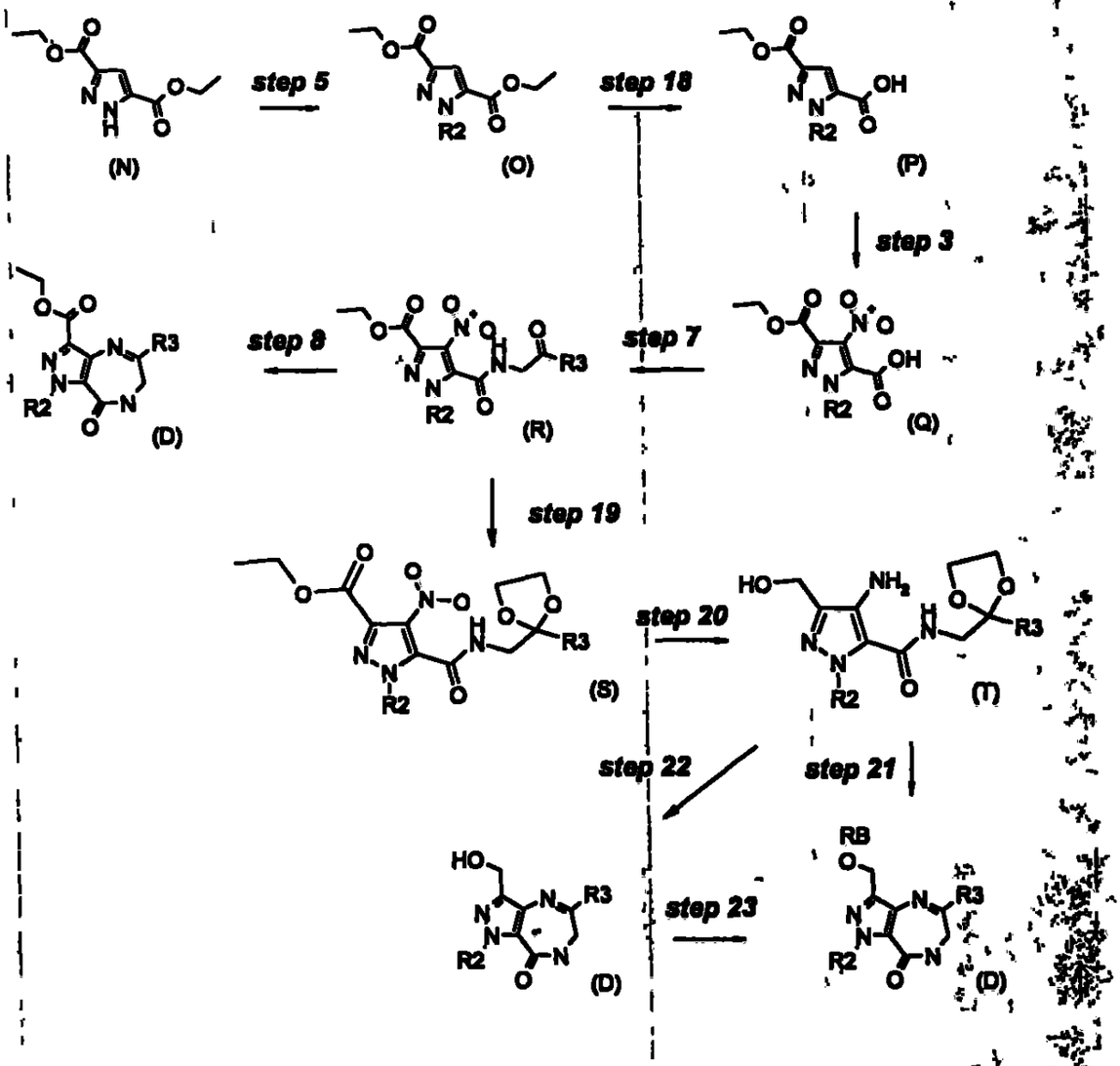
Reaction scheme 3

This scheme describes the synthesis of compounds D with R1 = $(CH_2)_nOR_B$ or $(CH_2)_nCOOR_B$ These molecules can lead, via standard reactions of organic chemistry, to the formation of compounds D with R1 = $(CH_2)_nC(O)R_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$ or $(CH_2)_nZ$ with n, R_A, R_B, R_C and Z as described above

Steps 3, 5, 7 and 8 are described above in general

Steps 5, 18, 3, 7 and 8 are illustrated by Example 5 and steps 19, 20 and 21 by Example 97

Reaction scheme 3



Step 22

This cyclization step is carried out in acidic medium, for example 5% HCl, in an aprotic solvent such as tetrahydrofuran, to give the hydroxy derivative D with R1 = CH_2OH

Step 23

This step leads to the synthesis of various derivatives D (R1=OR_8) using, for example, a compound of the type R_8-hal, in which R_8 is as defined above and hal is a halogen

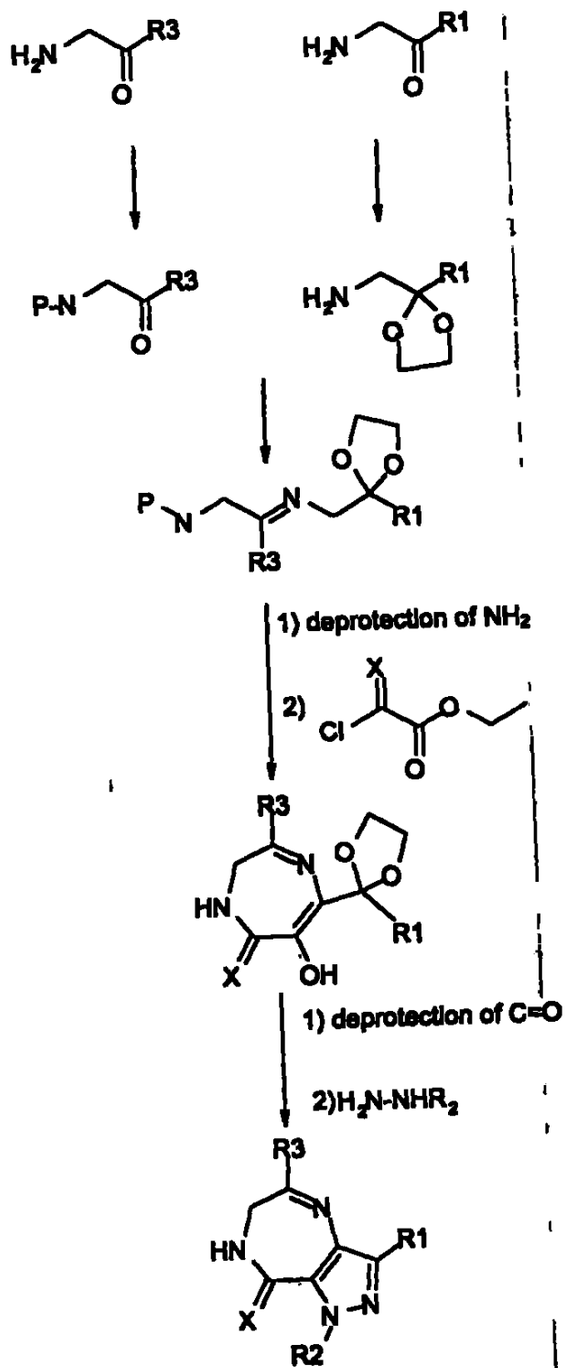
Step 21

This step is limited to the use of hydroxylated solvents such as MeOH and EtOH, during the cyclisation step of compound T, also allows the synthesis of compounds D with R1=OR_8

Reaction scheme 4

This is an alternative method for sythesizing the compounds of general formula I in which X is O or S and R1, R2 and R3 are as defined above This alternative method is illustrated in the scheme below

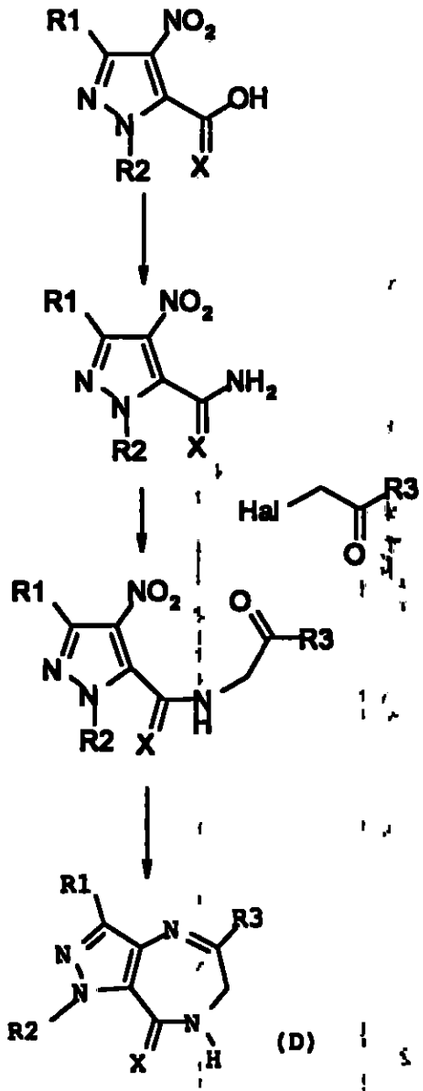
Reaction scheme 4



Reaction scheme 5

This is another method for synthesizing compounds of general formula I in which X is O or S This method is illustrated in summary in the scheme given below A more detailed description of this synthesis is presented in US patent 5 272 147, the content of which is incorporated into the present patent application by reference

Reaction scheme 5



EXAMPLES

EXAMPLE 1

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = isopropyl R2 = ethyl R3 = phenyl)

Step 1

0 37 g (0 0138 mol) of sodium is dissolved portionwise in 40 ml of anhydrous ethanol under nitrogen at room temperature 1 86 ml (13 6 mmol) of diethyl oxalate in 10 ml of anhydrous ethanol are added 1 47 ml (13 6 mmol) of isopropyl methyl ketone are added The reaction mixture is left stirring overnight at room temperature (RT) and is then evaporated to dryness The product obtained is isolated in the form of an orange powder (compound A1) m = 3 1 g (100%)

MS (ES+), m/z = 185

Rf (CH_2Cl_2/acetone 90/10) = 0 91

Step 2

0 98g (14 8 mmol) of potassium hydroxide is dissolved in 7 5 ml of water and the reaction medium is cooled to 0°C 3 1 g (14 8 mmol) of compound A1 (see scheme 1) are added portionwise and the mixture is stirred for 30 min at 0°C 1 94 g (14 8 mmol) of hydrazine sulphate are added and the mixture is then stirred for 45 min at 0°C After filtration, the precipitate is rinsed with a small amount of water and then dried to give 0 93 g (13%) of a white powder (compound A2)

^1H NMR (DMSO, 400 MHz)

1 2 ppm (6H, d), 2 95 ppm (1H, m) 6 45 ppm (1H, s) 12 3 ppm (1H, m)

Step 3

Method M1 is used 100 ml of concentrated H_2SO_4 are introduced into a round-bottomed flask The flask is cooled to 0°C and 10 09 g (0 065 mol) of compound A2 (see scheme 1)(0 065 mol) are added, followed by addition of 16 5 g (0 195 mol) of $NaNO_3$ The mixture is warmed to RT and stirred for 24 h The reaction medium is poured gently into 200 ml of ice-cold water, cooling the flask if necessary, and stirred for 30 min The precipitate is filtered off and rinsed with water After drying, 4 25 g (33%) of a white powder are obtained (compound A3)

MS (ES-) m/z = 198

^1H NMR (DMSO, 400 MHz)

1 3 ppm (6H, d), 3 5 ppm (1H, m) 13 9 ppm (2H, m)

Step 4

A mixture of 4 25 g of compound A3 (0 021 mol), 24 ml of ethanol and 2 3 ml of concentrated H_2SO_4 in a round-bottomed flask is refluxed for 4 5 h The reaction medium is evaporated and then taken up in CH_2Cl_2 and washed with water, after drying over $MgSO_4$, the organic phase is filtered and then concentrated to give 4 g (83%) of powder (compound A4)

MS (ES+), m/z = 228

Rf (CH_2Cl_2/MeOH 95/5) = 0 52

Step 5

Method M5 is used 2 77 g (0 02 mol) of K_2CO_3 are added under a stream of nitrogen to a solution of 4 g (0 02 mol) of compound A4 in 40 ml of anhydrous DMF, followed by addition of 1 76 ml (0 022 mol) of iodoethane The reaction medium is heated at 60°C for 16 5 h After filtering off the precipitate, the filtrate is taken up in diethylether (100 ml) and this organic phase is washed with water, dried over $MgSO_4$, filtered and then concentrated to give 4 g of an oily compound

This crude product is purified by flash chromatography on a column of silica using the following elution gradient from 50/50 CH_2Cl_2/heptane to 80/20 CH_2Cl_2/heptane to give 2 92 g (57%) of a yellow oil (compound A5)

MS (ES+), m/z = 256

^1H NMR ($CDCl_3$, 400MH_z)

1 3 ppm (6H, d) 1 35 ppm (3H, t) 1 45 ppm (3H, t) 3 45 ppm (1H, m) 4 2 ppm (2H, q) 4 45 ppm (2H, q)

Step 6

2 92 g (0 011 mol) of compound A5 (see scheme 1) are introduced into 15 ml of methanol in a round-bottomed flask, followed by addition of a solution of 0 68 g (0 0165 mol) of sodium hydroxide in 15 ml of water The mixture is stirred at RT for 3 h After evaporating off the methanol, the residue is taken up in CH_2Cl_2, an identical volume of water is added and the resulting mixture is then acidified (with stirring) with concentrated (36%) HCl After separation of the phases by settling, the organic phase is dried over Na_2SO_4 and concentrated to give 2 3 g of a white powder (92%) (compound A)

MS (ES-), m/z = 226

^1H NMR (DMSO, 400 MHz),

1 2 ppm (6H, d), 1 35 ppm (3H, t), 3 35 ppm (1H, m), 4 15 ppm (2H,q)

Step 7

Method M8 is used 1 g (4 mmol) of compound A (see scheme 1) is dissolved in a mixture of 25 7 ml of THF and 1 4 ml of DMF, followed by addition, under nitrogen, of 0 51 g (4 mmol) of N-hydroxysuccinimide The reaction medium is cooled to 0°C so as to add portionwise 0 91 g (4 mmol) of dicyclohexylcarbodiimide The mixture is stirred overnight at RT The precipitate formed is filtered off and the filtrate is evaporated to dryness The residue is taken up

in 20 ml of CH_2Cl_2, 0 75 g (4 mmol) of 2-aminoacetophenone hydrochloride is added under nitrogen, the reaction medium is cooled to 0°C, 0 61 ml (4 mmol) of triethylamine is then added and the mixture is stirred at RT for 3 h The reaction medium is poured into water with stirring After extraction with dichloromethane, washing with water and drying over Na_2SO_4, the organic phase is evaporated to dryness to give 1 3 g (86%) of a white powder (compound C)

MS (ES+), m/z = 345

^1H NMR ($CDCl_3$, 400MHz),

1 35 ppm (6H, d) 1 5 ppm (3H, q), 3 55 ppm (1H, m), 4 3 ppm (2H, q) 5 ppm (2H, d) 7 5 ppm (2H, t), 7 65 ppm (1H, d) 7 7 ppm (1H, m), 8 ppm (2H, d)

Step 8

Method M11 is used 1 3 g (3 7 mmol) of compound C (see scheme 1) are introduced into a mixture of 30 ml of ethanol and 7 ml of water in a round-bottomed flask, followed by addition of 2 2 g (3 9 mmol) of iron and 0 5 ml of conc (36%) HCl The reaction medium is refluxed for 1 h 15 min The iron is removed by filtration The filtrated is concentrated to dryness and the residue is taken up in CH_2Cl_2 and washed with twice 70 ml of water and then with saturated NaCl solution, the organic phase is dried over Na_2SO_4, filtered and concentrated to give an amorphous red powder (m = 0 9 g)

This crude product is purified by flash chromatography using the following elution gradient 98/2 CH_2Cl_2/acetone to 90/10 CH_2Cl_2/acetone

The red powder obtained after evaporation is taken up in the minimum amount of diethyl ether and then filtered After drying, 0 35 g (32%) of a beige powder (compound D) is isolated

MS (ES+), m/z = 297

m p = 157 2°C

^{1}H NMR ($CDCl_3$, 400MHz),

1 4 ppm (6H, d), 1 5 ppm (3H, t) 3 35 ppm (1H, m), 4 1 ppm (2H, d) 4 55 ppm (2H, q), 6 25 ppm (1H, m), 7 45 ppm (3H, m) 8 0 ppm (2H, m)

EXAMPLE 2

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione

(R1 = isopropyl, R2 = ethyl R3 = phenyl)

Step 9

0 2 g (0 67 mmol) of compound D (see scheme 1) is dissolved in 7 ml of toluene over sieves, and 0 54 g (1 34 mmol) of Lawesson's reagent is added, under nitrogen The mixture is refluxed for 16 5 h The reaction medium is cooled to RT, 2 ml of 5% HCl are then added, followed by 25 ml of methanol and 25 ml of cyclohexane, the mixture is stirred, the precipitate is then filtered off and the two phases are allowed to separate by settling The methanol phase is evaporated The residue is taken up in ethyl acetate and washed with water, the organic phase is dried over Na_2SO_4, filtered and evaporated

The crude product is purified by flash chromatography (80/20 cyclohexane/ethyl acetate) After evaporation, 0 15 g (75%) of a yellow powder (compound E) is obtained

MS (ES+), m/z = 313

m p = 164°C

^{1}H NMR ($CDCl_3$, 400 MHz),

1 4 ppm (6H, d), 1 5 ppm (3H, t), 3 3 ppm (1H, m), 4 2 ppm (2H, m), 4 8 ppm (2H, q), 7 45 ppm (3H, m), 8 ppm (2H, d) 8 3 ppm (1H, m)

EXAMPLE 3

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-ylidenecyanamide
(R1 = isopropyl R2 = ethyl R3 = phenyl)

Step 10

According to M13, 1 83 g (5 86 mmol) of 1-ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione are reacted with 0 18 g of 80% sodium hydride in refluxing THF for 1 h, and 0 44 ml of methyl iodide is then added at room temperature The mixture is refluxed for 2 h to give 1 53 g (80%) of the expected methylsulphanyl of type G (see Scheme 1)

m p = 98°C

MS (ES+), m/z = 327

^{1}H NMR (DMSO, 400 MHz),

8 1 ppm (2H, d) 7 4 ppm (3H, m), 4 4 ppm (4H, m), 3 2 ppm (1H, m), 2 4 ppm (3H, s), 1 4 ppm (3H, t), 1 3 ppm (6H, m)

Step 11

0 5g (1 53 mmol) of the methylsulphanyl G is reacted with 0 12 g (2 eq) of cyanamide to give 0 396 g (81%) of the expected product of type F (see Scheme 1)

m p = 222°C

MS (ES+), m/z = 321

^{1}H NMR (DMSO, 400 MHz),

9 4 ppm (1H, 1s) 8 ppm (2H, m), 7 4 ppm (3H, m), 4 3 ppm (2H, g), 4 1 ppm (2H, 1s), 3 1 ppm (1H, m), 1 3 ppm (3H, t) 1 2 ppm (6H, d)

EXAMPLE 4

1-Ethyl-3,5-diphenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
(R1 = phenyl, R2 = ethyl, R3 = phenyl)

Step 15

35 75 g (0 15 mol) of compound K (see scheme 2) in 35 ml of methanol are introduced into a round-bottomed flask, followed by addition of a solution of 9 24 g (0 231 mol) of sodium hydroxide in 140 ml of water The mixture is stirred at room temperature overnight After evaporation, the residue is taken up in ethanol and then filtered and dried to give 26 7 g (87%) of a beige powder (compound L, see scheme I)

MS (ES+), m/z = 203 9

^{1}H NMR (DMSO, 400 MHz)

4 7 ppm (2H, m), 7 2 ppm (1H, m) 7 3 ppm (2H, t), 7 75 ppm (2H, d), 12 2 ppm (1H, m)

Step 16

1 5 g (8 7 mmol) of 2-aminoacetophenone hydrochloride are dissolved in a mixture of 50 ml of THF and 10 ml of DMF, followed by addition of 1 22 ml (8 7 mmol) of triethylamine, 1 34 g (8 7 mmol) of 1-hydroxybenzotriazole hydrate and then 1 77 g (8 7 mmol) of compound L (see scheme 2) and finally 1 37 g (8 7 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide The mixture is heated at 60°C for 24 h The precipitate formed is filtered off and the filtrate is taken up in water After extraction with ethyl acetate, the extracts are washed with water and dried over Na_2SO_4 The organic phase is evaporated to dryness to give 1 8 g of an orange powder This crude product is purified by flash using the following elution gradient from CH_2Cl_2 to 95/5 CH_2Cl_2/methanol to give 0 45 g (16%) of a beige powder (compound M, see scheme 2)

MS (ES+), m/z = 303

^{1}H NMR (DMSO, 400 MHz)

4 15 ppm (2H, m) 7 3-7 55 ppm (6H, m) 8-8 1 ppm (4H, m), 8 3 ppm (1H, m) 14 ppm (1H, m)

Step 17

According to M5, 1 23 g (8 9 mmol) of K_2CO_3 are added, under a stream of nitrogen, to a solution of 2 7 g (8 9 mmol) of compound M (see scheme 2) in 30 ml of anhydrous DMF, followed by addition of 0 71 ml (8 9 mmol) of iodoethane The reaction medium is heated at 60°C overnight The reaction medium is extracted with diethyl ether, and the extracts are dried over Na_2SO_4, filtered and then concentrated to give 3 6 g of an oily compound

This crude product is purified by flash using the following elution gradient from CH_2Cl_2 to 98/2 CH_2Cl_2/acetone The oily product thus obtained is crystallized from diethyl ether to give 0 2 g (7%) of a yellow powder (compound (see scheme 2))

MS (ES+), m/z = 331

^1H NMR (DMSO, 400 MHZ)

1 4 ppm (3H, t) 4 1 ppm (2H, m) 4 5 ppm (2H, q) 7 3 ppm (1H, m) 7 4 ppm (2H, m) 7 5 ppm (3H, m), 8 ppm (4H, m) 8 5 ppm (1H, m)

EXAMPLE 5

Ethyl 1-ethyl-8-oxo-5-phenyl-1,6,7,8-tetrahydropyrazolo-[4,3-e][1,4]diazepin-3-carboxylate

(R1 = ethyl carboxylate, R2 = ethyl R3 = phenyl)

Step 5

20 g (94 mmol) of diethyl 3,5-pyrazoledicarboxylate (commercial) are reacted with 8 3 ml (103 mmol) of iodoethane to give 21 4 g (95%) of a pyrazole O (see Scheme 3)

Rf (95/5 CH_2Cl_2/MeOH) = 0 70

MS (ES+), m/z = 240 8

^1H NMR ($CDCl_3$, 400 MHz),

7 25 ppm (1H, s) 4 6 ppm (2H, q), 4 25-4 4 ppm (4H, m) 1 4 ppm (3H, t) 1 3 ppm (6H, m)

Step 18

21 g (87 mmol) of pyrazole O (see scheme 3) are reacted, under cold conditions, in 100 ml of water and 160 ml of THF with a solution of 3 84 g (96 mmol) of sodium hydroxide pellets in 100 ml of water After warming to room temperature, the reaction mixture is stirred for 2 hours The mixture is then extracted with diethyl ether The aqueous phase is acidified with 36% HCl down to pH = 2 and then extracted with dichloromethane The organic phase is dried over Na_2SO_4 and then filtered and concentrated to give 13 5 g (73%) of compound P(see scheme 3)

Rf (80/20 CH_2Cl_2/MeOH) = 0 55

MS (ES+), m/z = 212 8

^1H NMR ($CDCl_3$, 400 MHz),

9 1-9 5 ppm (1H, m), 7 4 ppm (1H, s), 4 65 ppm (2H, q), 4 35 ppm (2H, q), 1 4 ppm (3H, t), 1 3 ppm (3H, t)

Step 3

According to M3, 6 g (28 mmol) of compound P (see scheme 3) are reacted with 19 75 g (84 mmol) of copper nitrate hemipentahydrate in a mixture of trifluoroacetic anhydride and chloroform, to give 6 9 g (95%) of compound Q (see scheme 3)

Rf (80/20 CH_2Cl_2/MeOH + 0 3% HCOOH) = 0 46

MS (ES^-), m/z = 255 8

^1H NMR (DMSO, 400 MHz),

4 55 ppm (2H, q), 4 3 ppm (2H, q) 1 4 ppm (3H, t), 1 3 ppm (3H,t)

Step 7

According to M8, 3 g (11 7 mmol) of compound Q (see scheme 3) are reacted with 2 g (11 7 mmol) of 2-aminoacetophenone hydrochloride to give 4 38 g of compound R (see Scheme 3)

MS (ES+), m/z = 372 8

^{1}H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (3H, m) 7 55 ppm (1H, m) 7 45 ppm (2H, m), 4 9 ppm (2H, d), 4 3-4 5 ppm (4H, m), 1 45 ppm (3H, t) 1 35 ppm (3H, t)

Step 8

According to M11, 1 g (2 7 mmol) of compound R (see scheme 3) is refluxed with 0 3 g (5 4 mmol) of iron and 0 27 ml of 36% HCl in a mixture of ethanol and water to give 0 1 g (12%) of the expected compound D (see Scheme 3)

Rf (50/50 cyclohexane/EtOAc) = 0 19

SM (ES^+), m/z = 327

^{1}H NMR ($CDCl_3$, 400 MHz),

8 55 ppm (1H, m), 8 05 ppm (2H, m), 7 55 ppm (3H, m) 4 55 ppm (2H, q) 4 3 ppm (2H, q), 4 1 ppm (2H, d), 1 4 ppm (3H, t) 1 3 ppm (3H, t)

EXAMPLE 6

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl, R3 = 4-methoxyphenyl)

Step 7

According to M8, 0 5 g (2 5 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (see *J Med Chem* , 16, 1973, 1346-1354 or USP 3 700 657) is reacted with 0 5 g of 2-amino-4'-methoxyacetophenone hydrochloride to give 0 78 g (90%) of an amide of type C (see Scheme 1)

m p 151°C

Analysis calculated for $C_{16}H_{18}N_4O_5$

C, 55 49, H, 5 24, N, 16 11 O, 23 10

found C, 55 45 H, 5 44, N, 16 09, O, 22 9

Step 8

Acording to M11, 0 6 g (1 73 mmol) of the amide C (see scheme 1) is refluxed with 1 04 g of iron and 0 173 ml of 36% HCl in an ethanol/water mixture to give 0 35 g (70%) of the expected product D (see scheme 1)

m p 178°C

MS (ES^+), m/z = 299

^1H NMR ($CDCl_3$, 400 MHz),

7 8 ppm (2H, d) 6 9 ppm (2H, d) 6 0 ppm (1H, t), 4 5 ppm (2H, q) 4 2 ppm (2H, d) 3 8 ppm (3H, s) 2 4 ppm (3H, s) 1 45 ppm (3H, t)

EXAMPLE 7

5-(4-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl, R2 = ethyl, R3 = 4-bromophenyl)

Step 7

According to M8, 0 5 g (2 5 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 51 g of 2-amino-4'-bromoacetophenone hydrochloride to give 0 57 g (60%) of an amide of type C (see Scheme 1)

m p 184°C,

^1H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (1H, s) 7 8 ppm (2H, d), 7 6 ppm (2H, d), 4 9 ppm (2H, s) 4 3 ppm (2H, q) 2 5 ppm (3H, s), 1 5 ppm (3H, t)

Analysis calculated for $C_{15}H_{15}BrN_4O_4$

C, 45 59 H, 3 83 Br, 20 22 N, 14 18 O, 16 19

found C, 45 42 H, 3 74, Br, 19 99 N, 14 11, O, 16 22

Step 8

According to M11, 0 475 g (1 2 mmol) of the amide C (see scheme 1) is refluxed with 0 721 g of iron and 0 12 ml of 36% HCl in an ethanol/water mixture to give 0 25 g (60%) of the expected product D (see Scheme 1)

m p 223°C

MS (ES^+), m/z = 348

^1H NMR ($CDCl_3$, 400 MHz),

7 8 ppm (2H, d) 7 5 ppm (2H, d), 6 2 ppm (1H, s) 4 5 ppm (2H, q) 4 0 ppm (2H, s) 2 3 ppm (3H, s) 1 4 ppm(3H, t)

EXAMPLE 8

1-Ethyl-3-methyl-5-naphth-2-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl, R3 = naphthyl)

Step 7

According to M8, 0 45 g (2 25 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 5 g of 2-amino-1-naphth-2-yl-ethanone hydrochloride to give 0 588 g (75%) of an amide of type C (see Scheme 1)

Rf (5/5 cyclohexane/EtOAc) = 0 25

^1H NMR ($CDCl_3$, 400 MHz),

8 6 ppm (1H, t) 8 0 ppm (7H, m) 5 15 ppm (2H, d), 4 4 ppm (2H, q) 2 6 ppm (3H, s) 1 5 ppm (3H, t)

Step 8

0 58 g (1 58 mmol) of amide C (see scheme 1) is refluxed with 0 948 g of iron and 0 158 ml of 36% HCl in an ethanol/water mixture to give 0 32 g (79%) of the expected product D (see Scheme 1)

m p 193°C

MS (ES^+), m/z = 319

^1H NMR ($CDCl_3$, 400 MHz),

8 2 ppm (2H, m), 7 8 ppm (3H, m), 7 5 ppm (2H, m), 6 4 ppm (1H, t), 4 5 ppm (2H, q) 4 2 ppm (2H, d), 2 4 ppm (3H, s) 1 45 ppm (3H, t)

EXAMPLE 9

5-(3-Chlorothien-2-yl)-1-ethyl-3-methyl-6,7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl R3 = chlorothienyl)

Step 7

According to M8, 0 235 g (1 18 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 5 g of 2-amino-1-(3-chlorothien-2-yl)ethanone hydrochloride to give 0 32 g (76%) of an amide of type C (see Scheme 1) in which R1, R2 and R3 are as defined in this example

Rf (5/5 cyclohexane/EtOAc) = 0 53

^{1}H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (1H, m) 7 7 ppm (1H, d) 7 1 ppm (1H, d) 5 0 ppm (2H, d) 4 45 ppm (2H, q), 2 6 ppm (3H, s) 1 5 ppm (3H, t)

Step 8

According to M11, 0 31 g (0 87 mmol) of the amide C (see scheme 1) is refluxed with 0 52 g of iron and 0 087 ml of 36% HCl in an ethanol/water mixture to give 0 135 g (50%) of the expected product D (see Scheme 1)

m p 213°C

MS (ES^+), m/z = 309

^{1}H NMR ($CDCl_3$, 400 MHz),

7 4 ppm (1H, d) 6 9 ppm (1H, d), 6 1 ppm (1H, t), 4 55 ppm (2H, q) 4 3 ppm (2H, d) 2 4 ppm (3H, s) 1 45 ppm (3H, t)

EXAMPLE 10

Methyl 3-(1-ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-e][1,4]diazepin-5-yl)propanoate

(R1 = methyl, R2 = ethyl, R3 = methyl propanoate)

Step 7

According to M8, 0 44 g (2 21 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 41 g (1 eq) of methyl 5-amino-4-oxopentanoate

hydrochloride to give 0 63 g (87%) of an amide of type C (see scheme 1)

Rf (95/5 CH_2Cl_2/methanol) = 0 48

^1H NMR ($CDCl_3$, 400 MHz),

7 7 ppm (1H, m) 4 4 ppm (2H, d) 4 3 ppm (2H, q), 3 7 ppm (3H, s) 2 85 ppm (2H, dd) 2 7 ppm (2H, dd), 2 5 ppm (3H, s) 1 5 ppm (3H, t)

Step 8

According to M11, 0 6 g (1 83 mmol) of the amide C (see scheme 1) is refluxed with 1 1 g of iron and 0 18 ml of 36% HCl in an ethanol/water mixture to give 0 42 g (83%) of the expected product D (see scheme 1)

m p 68°C

^1H NMR ($CDCl_3$, 400 MHz),

6 7 ppm (1H, t), 4 5 ppm (2H, q), 3 8 ppm (3H, s) 3 55 ppm (2H, d), 2 85 ppm (2H, t), 2 7 ppm (2H, t), 2 2 ppm (3H, s) 1 45 ppm (3H, t)

EXAMPLE 11

5-(4-Chlorophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

R1 = methyl R2 = ethyl, R3 = 4-chlorophenyl

Step 7

According to M8, 0 5 g (2 5 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 517 g (1 eq) of 2-amino-4'-chloroacetophenone hydrochloride to give 0 5 g (57%) of an amide of type C (see scheme 1) in which R1, R2 and R3 are as defined in this example Rf (5/5 cyclohexane/EtOAc) = 0 55

^1H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (3H, d) 7 5 ppm (2H, d) 4 95 ppm (2H, d), 4 35 ppm (2H, q) 2 5 ppm (3H, s), 1 5 ppm (3H, t)

Step 8

According to M11, 0 45 g (1 28 mmol) of the amide C (see scheme 1) is refluxed with 0 77 g of iron and 0 128 ml of 36% HCl in an ethanol/water mixture to give 0 27 g (70%) of the expected product D (see Scheme 1)

m p 215°C

MS (ES^+), m/z = 303

^1H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (2H, d) 7 5 ppm (2H, d), 6 ppm (1H, t), 4 5 ppm (2H, q), 4 1 ppm (2H, d) 2 4 ppm (3H, s) 1 45 ppm (3H, t)

EXAMPLE 12

5-(4-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo-[4,3-e][1,4]diazepin-8-one

(R1 = methyl, R2 = ethyl, R3 = 4-aminophenyl)

Step 7

According to M8, 0 5 g (2 5 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 540 g (1 eq) of 2-amino-4'-nitroacetophenone hydrochloride to give 0 45 g (50%) of an amide of type C (see scheme 1)

Rf (EtOAc) = 0 9

^1H NMR ($CDCl_3$, 400 MHz),

8 4 ppm (2H, d) 8 2 ppm (2H, d), 8 0 ppm (1H, m), 5 0 ppm (2H, d), 4 4 ppm (2H, q) 2 5 ppm (3H, s) 1 5 ppm (3H, t)

Step 8

According to M11, 0 38 g (1 05 mmol) of the amide C (see scheme 1) is refluxed with 0 63 g of iron and 0 105 ml of 36% HCl in an ethanol/water mixture to give 0 12 g (40%) of the expected product D (see scheme 1)

m p 212°C

MS (ES^+), m/z = 284

^1H NMR (DMSO, 400 MHz),

8 2 ppm (1H, t) 7 8 ppm (2H, d), 6 6 ppm (2H, d), 5 8 ppm (2H, s) 4 5 ppm (2H, q) 3 9 ppm (2H, d), 2 3 ppm (3H, s), 1 45 ppm (3H, t)

EXAMPLE 13

1-Ethyl-5-(4-fluorophenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl, R2 = ethyl, R3 = 4-fluorophenyl)

Step 7

According to M8, 0 1 g (0 53 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 1 g of 2-amino-4'-fluoroacetophenone hydrochloride to give 0 17 g (96%) of an amide of type C (see scheme 1)

Rf (5/5 cyclohexane/EtOAc) = 0 45

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, m) 7 9 ppm (1H, m) 7 15 ppm (2H, m), 4 95 ppm (2H, d), 4 3 ppm (2H, q) 2 5 ppm (3H, s) 1 5 ppm (3H, t)

Step 8

According to M11, 0 16 g (0 48 mmol) of the amide C (see scheme 1) is refluxed with 0 287 g of iron and 0 048 ml of 36% HCl in an ethanol/water mixture to give 0 08 g of the expected product D (see scheme 1)

m p 174 C

MS (ES^+), m/z = 287

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, m) 7 15 ppm (2H, m), 6 7 ppm (1H, t), 4 5 ppm (2H, q), 4 1 ppm (2H, d), 2 4 ppm (3H, s), 1 5 ppm (3H, t)

EXAMPLE 14

5-(3-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo-[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl R3 = 3-bromophenyl)

Step 7

According to M8, 0 08 g (0 4 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 1 g (1 eq) of 2-amino-3'-bromoacetophenone hydrochloride to give 0 16 g (100%) of an amide of type C (see scheme 1)

Rf (98/2 CH_2Cl_2/MeOH) = 0 29

^1H NMR ($CDCl_3$, 400 MHz),

8 15 ppm (1H, s) 7 9 ppm (2H, m), 7 8 ppm (1H, m), 7 4 ppm (1H, m) 5 0 ppm (2H, d), 4 3 ppm (2H, q) 2 6 ppm (3H, s), 1 5 ppm (3H, t)

Step 8

According to M11, 0 16 g (0 4 mmol) of the amide C is refluxed with 0 24 g of iron and 0 04 ml of 36% HCl in an ethanol/water mixture to give 0 06 g (43%) of the expected product D (see scheme)

m p 173°C

MS (ES^+), m/z = 348

^1H NMR ($CDCl_3$, 400 MHz),

8 1 ppm (1H, m) 7 9 ppm (1H, m), 7 6 ppm (1H, m), 7 4 ppm (1H, m), 7 25 ppm (1H, s), 6 3 ppm (1H, t), 4 6 ppm (2H, q), 4 1 ppm (2H, d), 2 4 ppm (3H, s), 1 5 ppm (3H, t)

EXAMPLE 15

3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one

(R1 = methyl R2 = propyl, R3 = phenyl)

Step 7

According to M8, 0 37 g (1 6 mmol) of 5-methyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid is reacted with 0 28 g (1 6 mmol) of 2-aminoacetophenone hydrochloride to give 0 54 g (96%) of an amide of type C (see scheme 1)

Rf (90/10) CH_2Cl_2/acetone) = 0 7

^1H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, d), 7 85 ppm (1H, t), 7 65 ppm (1H, m), 7 55 ppm (2H, m) 5 0 ppm (2H, d) 4 25 ppm (2H, t), 2 55 ppm (3H, s) 1 9 ppm (2H, m) 0 9 ppm (3H, t)

Step 8

According to M11, 0 138 g (0 42 mmol) of the amide C (see scheme 1) is refluxed with 0 28 g of iron and 0 05 ml of 36% HCl in an ethanol/water mixture to give 0 072 g (61%) of the expected product D (see scheme 1)

m p 171°C

MS (ES^+), m/z = 283

^1H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, d) 7 55 ppm (3H, m) 6 65 ppm (1H, t), 4 5 ppm (2H, t) 4 15 ppm (2H, d), 2 4 ppm (3H, s) 1 9 ppm (2H, m) 0 9 ppm (3H, t)

EXAMPLE 16

1-(2-Hydroxyethyl)-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

(R1 = methyl R2 = 2-hydroxyethyl, R3 = phenyl)

Step 5

6 3 g (33 8 mmol) of a pyrazole of type A4 (see scheme 1 and *J Org Chem*, 21, 833-835, 1956 *Gazz Chim Ital*, 75, 121-131, 1945) are reacted with 8 48 g (40 5 mmol) of 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (commercial) to give 3 44 g (31%) of a pyrazole A5 (see scheme 1)

Rf (95/5 CH_2Cl_2/acetone) = 0 47

^1H NMR ($CDCl_3$, 400 MHz),

4 55-4 35 ppm (5H, m), 4 0 ppm (1H, m), 3 7-3 4 ppm (3H, m), 2 5 ppm (3H, s), 1 8-1 55 ppm (6H, m) 1 5 ppm (3H, t)

Step 6

1 1 g (3 4 mmol) of the pyrazole A5 (see scheme 1) are reacted with 0 2 g (5 1 mmol) of sodium hydroxide in a

mixture of methanol and water to give 0 97 g (95%) of a pyrazole of type A (see scheme 1)

Rf (80/20 CH_2Cl_2/MeOH) = 0 26

^1H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (1H, s) 4 7-4 5 ppm (3H, m), 4 0 ppm (1H, m), 3 8-3 45 ppm (3H, m), 2 5 ppm 3H, s), 1 9-1 4 ppm (6H, m)

Step 7

According to M8, 0 9 g (3 mmol) of 2-(2-hydroxyethyle)-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 52 g (3 mmol) of 2-aminoacetophenone hydrochloride to give 1 43 g (100%, crude) of an amide of type C (see scheme 1)

Rf (90/10 CH_2Cl_2/acetone) = 0 51

^1H NMR ($CDCl_3$, 400 MHz),

8 3 ppm (1H, s) 8 0 ppm (2H, m), 7 6 ppm (1H, m), 7 5 ppm (2H, m), 4 7 ppm (1H, m) 4 5 ppm (2H, t) 4 1 ppm (1H, m), 3 85 ppm (1H, m) 3 7-3 4 ppm (2H, m), 2 55 ppm (3H, s), 1 9-1 4 ppm (6H, m)

Step 8

According to M11, 1 4 g (3 mmol) of the amide C (see scheme 1) are refluxed with 1 8 g of iron and 0 31 ml of 36% HCl in a mixture of ethanol and water to give 0 09 g (11%) of the expected product D (see scheme 1)

m p 75°C

MS (ES^+), m/z = 285

^1H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, m), 7 55 ppm (3H, m) 7 05 ppm (1H,t), 4 65 ppm (2H, t) 4 15 ppm (2H, d), 4 0 ppm (2H, m) 3 9 ppm (1H, OH) 2 4 ppm (3H, s)

EXAMPLE 17

1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione

(R1 = methyl R2 = ethyl R3 = phenyl)

Step 9

0 2 g (0 74 mmol) of a pyrazolodiazepine of type D (see scheme 1), in which R1, R2 and R3 are as defined in this example, is refluxed in toluene with 0 6 g (2 eq) of Lawesson's reagent to give 188 mg (89%) of the expected product E (see scheme 1)

m p 203 5°C

MS (ES^+), m/z = 285

^1H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, m) 7 8 ppm (1H, t), 7 5 ppm (3H, m) 4 8 ppm (2H, q) 4 25 ppm (2H, d) 2 5 ppm (3H, s) 1 6 ppm (3H, t)

EXAMPLE 18

1-Ethyl-5-(3-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl, R2 = ethyl R3 = 3-methoxyphenyl)

Step 7

According to M8, 0 5 g (2 51 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 51 g (2 51 mmol) of 2-amino-3'-methoxyacetophenone hydrochloride (Patent, Brachwitz, Werner, DD65929, 1967) to give 0 8 g (92%) of an amide of type C (see scheme 1)

Rf (CH_2Cl_2/MeOH 90/10) = 0 87

^1H NMR ($CDCl_3$, 400 MHz),

7 95 ppm (1H, s) 7 55 ppm (1H, m) 7 5 ppm (1H, m) 7 4 ppm (1H, m) 7 2 ppm (1H, m), 5 0 ppm (2H, d) 4 35 ppm (2H, q), 3 9 ppm (3H, s) 2 55 ppm (3H, s), 1 5 ppm (3H, t)

Step 8

According to M11, 0 792 g (2 29 mmol) of the amide C (see scheme 1) is refluxed with 1 37 g of iron and 0 23 ml of 36% aqueous HCl in an ethanol/water mixture to give 0 312 g (46%) of the expected product D (see scheme 1)

m p 120°C

MS (ES^+), m/z = 299

^1H NMR ($CDCl_3$, 400 MHz),

7 6-7 3 ppm (3H, m), 7 0 ppm (1H, m) 6 9 ppm (1H,s), 4 6 ppm (2H, q) 4 1 ppm (2H, d), 3 9 ppm (3H, s), 2 4 ppm (3H, s), 1 5 ppm (3H, t)

EXAMPLE 19

5-(2-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl, R2 = ethyl R3 = 2-aminophenyl)

Step 7

According to M8, 1 11 g (5 56 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid are reacted with 0 5 g of 2-amino-2'-nitroacetophenone hydrochloride to give 0 246 g (44%) of an amide of type C (see scheme 1

Rf (CH_2Cl_2/MeOH 90/10) = 0 87

^1H NMR ($CDCl_3$, 400 MHz),

9 3 ppm (1H, s), 8 2 ppm (1H, m) 7 8 ppm (1H, m); 7 6-7 5 ppm (2H, m) 4 6 ppm (2H, d), 4 1 ppm (2H, q), 2 5 ppm (3H, s), 1 4 ppm (3H, t)

Step 8

According to M11, 0 237 g (0 66 mmol) of the amide C (see scheme 1) is refluxed with 0 4 g of iron and 0 07 ml of 36% HCl in an ethanol/water mixture to give 0 08 g (43%) of the expected product D (see scheme 1)

m p 156°C

MS (ES^+), m/z = 284

^{1}H NMR($CDCl_3$, 400 MHz),

7 5 ppm (1H, m) 7 2 ppm (1H, m) 6 8-6 5 ppm (5H, m), 4 6 ppm (2H, q) 4 15 ppm (2H, d), 2 4 ppm (3H, s), 1 5 ppm (3H, t)

EXAMPLE 20

1-Ethyl-5-(2-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

(R1 = methyl, R2 = ethyl, R3 = 2-methoxyphenyl)

Step 7

According to M8, 0 24 g (1 22 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 245 g (1 22 mmol) of 2-amino-2'-methoxyoacetophenone hydrochloride (*J Org Chem*, 37, 2494-2496, 1972) to give 0 197 g (47%) of an amide of type C (see scheme 1)

Rf (CH_2Cl_2/MeOH 95/5) = 0 8

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (1H, m), 7 9 ppm (1H, CONH), 7 55 ppm (1H, m), 7 05 ppm (2H, m), 4 95 ppm (2H, d) 4 35 ppm (2H, q), 4 0 ppm (3H, s), 2 55 ppm (3H, s) 1 5 ppm (3H, t)

Step 8

According to M8, 0 19 g (0 55 mmol) of the amide C (see scheme 1) is refluxed with 0 33 g of iron and 0 055 ml of 36% HCl in an ethanol/water mixture to give 0 07 g (43%) of the expected product D (see scheme 1)

m p 214°C

MS (ES^+), m/z 299

^{1}H NMR ($CDCl_3$, 400 MHz),

7 75 ppm (1H, m) 7 4 ppm (1H, m), 7 1 ppm (1H, m), 7 0 ppm (1H, m), 6 45 ppm (1H s) 4 6 ppm (2H, q) 4 0 ppm (2H, d); 3 9 ppm (3H, s), 2 4 ppm (3H, s) 1 5 ppm (3H, t)

EXAMPLE 21

3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

(R1 = *tert*-butyl, R2 = ethyl R3 = phenyl)

Step 3

According to M1, 9 g (46 mmol) of ethyl 5-*tert*-butyl-*2H*-pyrazole-3-carboxylate and 11 61 g of $NaNO_3$ are reacted in 90 ml of concentrated H_2SO_4 to give 4 5 g (41%, white powder) of a compound of type A4 (see scheme 1)

MS (ES-), m/z = 240

Rf (CH_2Cl_2/acetone 90/10) = 0 54

Step 5

According to M5, 4 8 g (19 8 mmol) of compound A7 (see scheme 1) are reacted with 1 74 ml (22 mmol) of iodoethane to give 4 g of a compound of type A5 (see Scheme 1) (yellow oil, 75%)

MS (ES+), m/z = 270

^{1}H NMR ($CDCl_3$, 400 MHz),

1 35 ppm (12H, m) 1 4 ppm (3H, t) 4 35 ppm (4H, q)

Step 6

4 g (14 8 mmol) of compound A5 (see scheme 1) are reacted with 0 89 g (22 mmol) of sodium hydroxide dissolved in a methanol/water mixture to give 3 2 g of a compound of type A (see scheme 1)(white powder, 89%)

MS (ES-), m/z = 240

^{1}H NMR (DMSO, 400 MHz),

1 05 ppm (9H, s), 1 1 ppm (3H, t) 4 05 ppm (2H, q), 14 4 ppm (1H, m)

Step 7

According to M8, 1 g (4 1 mmol) of compound A (see scheme 1) is reacted with 0 7 g of 2-amino-acetophenone hydrochloride to give 1 3 g (88%) of a compound of type C (see scheme 1)

MS (ES+), m/z = 359

^{1}H NMR ($CDCl_3$, 400 MHz)

1 45 ppm (9H, s) 1 5 ppm (3H, t) 4 2 ppm (2H, q), 4 95 ppm (2H, d), 7 4 ppm (1H, m) 7 55 ppm (2H, m), 7 65 ppm (1H, t) 8 0 ppm (2H, d)

Step 8

According to M11, 1 3 g (3 6 mmol) of compound C (see scheme 1) are refluxed with 0 5 ml of HCl and 2 16 g of iron in an ethanol/water mixture to give 0 2 g (18%) of the expected product D (see scheme 1)

MS (ES+), m/z = 311

m p = 160 C

^{1}H NMR ($CDCl_3$, 400 MHz),

1 5 ppm (12H, m), 4 1 ppm (2H, d), 4 55 ppm (2H, q) 6 7 ppm (1H, m), 7 45 ppm (3H, m), 8 0 ppm (2H, d)

EXAMPLE 22

3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione

(R1 = methyl, R2 = propyl R3 = phenyl)

Step 9

0 57 g (2 mmol) of 3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is refluxed in toluene with 1 6 g (4 mmol) of Lawesson's reagent to give 0 58 g (97%) of a compound of type E (see scheme 1)

MS (ES+), m/z = 299

^{1}H NMR ($CDCl_3$, 400 MHz)

0 9 ppm (3H, t) 1 95 ppm (2H, m) 2 4 ppm (3H, s), 4 2 ppm (2H, m), 4 75 ppm (2H, t), 7 4 ppm (3H, m), 7 95 ppm (2H, d), 8 65 ppm (1H, m)

m p 156°C

EXAMPLE 23

1-Ethyl-3-methyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = methyl, R2 = ethyl, R3 = *p*-tolyl)

Step 7

According to M8, 0 31 g (1 56 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 29 g (1 56 mmol) of 2-amino-4'-methylacetophenone hydrochloride to give 0 5 g (98%) of an amide of type C (see scheme 1)

Rf (CH_2Cl_2/MeOH 90/10) = 0 85

^{1}H NMR($CDCl_3$, 400 MHz),

7 9 ppm (3H, m), 7 3 ppm (2H, m), 4 95 ppm (2H, d), 4 35 ppm (2H, q), 2 55 ppm (3H, s), 2 45 ppm (3H, s), 1 5 ppm (3H, t)

Step 8

According to M11, 0 5 g (1 51 mmol) of the amide C (see scheme 1) is refluxed with 0 94 g of iron and 0 17 ml of 36% HCl in an ethanol/water mixture to give 0 15 g (34%) of the expected product D (see scheme 1)

m p 185°C

MS (ES^+), m/z = 283

^{1}H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (2H, d), 7 25 ppm (2H, d), 6 5 ppm (1H, s), 4 6 ppm (2H, q), 4 1 ppm (2H, d), 2 4 ppm (6H, s), 1 5 ppm (3H, t)

EXAMPLE 24

5-(3-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = methyl, R2 = ethyl, R3 = 3-aminophenyl)

Step 7

According to M8, 0 92 g (4 62 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 1 g

(4 62 mmol) of 2-amino-3'-nitroacetophenone hydrochloride to give 1 3 g (78%) of an amide of type C (see scheme 1)

Rf (CH_2Cl_2/MeOH 90/10) = 0 89

^1H NMR ($CDCl_3$, 400 MHz),

9 1 ppm (1H, s), 8 8 ppm (1H, s), 8 4 ppm (1H, m), 8 5 ppm (1H, m), 7 8 ppm (1H, m), 4 95 ppm (2H, d), 4 3 ppm (2H, q), 2 5 ppm (3H, s), 1 5 ppm (3H, t)

Step 8

According to M11, 1 3 g (3 6 mmol) of the amide C (see scheme 1) are refluxed with 2 15 g of iron and 0 38 ml of 36% HCl in an ethanol/water mixture to give 0 34 g (34%) of the expected product D (see scheme 1)

m p 80°C

MS (ES^+), m/z = 284

^1H NMR ($CDCl_3$, 400 MHz),

7 35 ppm (1H, m), 7 2 ppm (2H, m), 6 8 ppm (2H,m), 4 6 ppm (2H, q), 4 05 ppm (2H, d), 3 8 ppm (2H, bs), 2 4 ppm (3H, s); 1 5 ppm (3H, t)

EXAMPLE 25

3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-thione

(R1 = *tert*-butyl, R2 = ethyl, R3 = phenyl)

Step 9

0 37 g (2 2 mmol) of 3-*tert*-butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is reacted with 0 96 g (4 4 mmol) of Lawesson's reagent to give 0 25 g of a yellow powder (66%)

MS (ES+), m/z = 327

m p = 230°C

^1H NMR ($CDCl_3$, 400 MHz)

1 45 ppm (9H, s) 1 5 ppm (3H, m) 4 2 ppm (2H, m) 4 8 ppm (2H, q), 7 45 ppm (3H, m) 8 0 ppm (2H, d) 8 55 ppm (1H, m)

Example 26

5-(4-Aminophenyl)-3-tert-butyl-1-ethyl-6,7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = *tert*-butyl, R2 = ethyl R3 = 4-aminophenyl)

Step 7

According to M8, 1 2 g (4 9 mmol) of 5-*tert*-butyl-2-ethyl-4-nitro-2H-pyrazole-3-carboxylic acid are reacted with 1 06 g of 2-amino-4'-nitroacetophenone hydrochloride to give 1 15 g (58%) of an amide of type C (see scheme 1)

MS (ES-), m/z = 402

^{1}H NMR ($CDCl_3$, 400 MHz),

1 4 ppm (9H, s), 1 5 ppm (3H, t) 4 25 ppm (2H, q) 4 95 ppm (2H, d) 7 4 ppm (1H, m) 8 15 ppm (2H, d), 8 35 ppm (2H, d)

Step 8

According to M11, 1 15 g (2 8 mmol) of the amide C (see scheme 1) are refluxed with 0 5 ml of HCl and 1 7 g of iron in an ethanol/water mixture to give 0 43 g (48%) of the expected compound D (see scheme 1)

MS (ES+), m/z = 326

m p = 189°C

^{1}H NMR ($CDCl_3$, 400 MHz),

1 45 ppm (12H, m), 3 95 ppm (2H, s), 4 05 ppm (2H, d), 4 5 ppm (2H, q) 6 2 ppm (1H, m) 6 65 ppm (2H, d), 7 8 ppm (2H, d)

EXAMPLE 27

5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = isopropyl R2 = ethyl R3 = 4-aminophenyl)

Step 7

According to M8, 1 3 g (4 9 mmol) of 2-ethyl-5-isopropyl-4-nitro-2*H*-pyrazole-3-carboxylic acid are reacted with 1 23 g of 2-amino-4 -nitro-acetophenone hydrochloride to give 2 g (90%) of the amide of type C (see scheme 1)

MS (ES-), m/z = 388

^{1}H NMR ($CDCl_3$, 400 MHz),

1 3 ppm (9H, s) 1 5 ppm (3H, t) 3 55 ppm (1H, q) 4 3 ppm (2H, q) 5 ppm (2H, d) 7 8 ppm (1H, m) 8 15 ppm (2H, d), 8 4 ppm (2H, d)

Step 8

According to M11, 2 g (5 1 mmol) of the amide C (see scheme 1) are refluxed with 0 5 ml of HCl and 3 07 g of iron in an ethanol/water mixture to give 0 5 g (31%) of the compound of type D (see scheme 1)

MS (ES+), m/z = 312

m p = 191°C

^{1}H NMR (DMSO, 400 MHz),

1 15 ppm (6H, m) 1 25 ppm (3H, m) 3 05 ppm (1H, q) 3 8 ppm (2H, d) 4 3 ppm (2H, q) 5 65 ppm (2H m) 6 5 ppm (2H, d) 7 6 ppm (2H, d) 8 ppm (1H, m)

Example 28

1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1H-pyrazolo [4,3-e][1,4]diazepin-8-one
(R1 = methyl R2 = ethyl R3 = 4-hydroxyphenyl)

17 ml of a molar solution of BBr_3 in dichloromethane are added dropwise to a solution of 0 2 g of 1-ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one in 84 ml of dichloromethane The

resulting mixture is refluxed for 6 hours After cooling to RT, the reaction medium is neutralized with sodium bicarbonate solution The organic phase is dried and evaporated The product is purified by flash chromatography (gradient CH_2Cl_2, 90/10 CH_2Cl_2/acetone, 80/20 CH_2Cl_2/acetone) Evaporation of the solvent gives 0 103 g of compound D in the form of a beige powder (54%)

Rf (90/10 CH_2Cl_2/MeOH) = 0 25

^1H NMR (DMSO, 400 MHz),

9 5 ppm (1H, OH) 7 9 ppm (2H, m), 7 8 ppm (1H, bs) 6 9 ppm (2H, m) 4 5 ppm (2H, q) 4 ppm (2H, d) 2 4 ppm (3H, s) 1 5 ppm (3H, t)

MS (ES+) m/z = 285

m p = 250 C

EXAMPLE 29

5-(4-Aminophenyl)-3-methyl-1-propyl-6,7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = propyl R3 = 4-aminophenyl)

Step 7

According to M8, 1 5 g (7 mmol) of 5-methyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) are reacted with 1 52 g (7 mmol) of 2-amino-4'-nitro-acetophenone hydrochloride to give 2 5 g (95%) of an amide of type C (see scheme 1)

Rf (5/5 cyclohexane/ethyl acetate) = 0 5

^1H NMR ($CDCl_3$, 400 MHz),

8 4 ppm (2H, d) 8 2 ppm (2H, d) 8 ppm (1H, m) 5 ppm (2H, d) 4 25 ppm (2H, t) 2 55 ppm (3H, s), 1 9 ppm (2H, m) 0 95 ppm (3H, t)

Step 8

According to M11, 2 5 g (6 7 mmol) of the amide C (see scheme 1) are refluxed with 4 1 g of iron and 0 83 ml of

36% HCl in an ethanol/water mixture to give 0 75 g (40%) of the expected product D (see scheme 1)

m p 225°C

MS (ES+), m/z = 298

^{1}H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (1H, m) 7 8 ppm (2H, d) 6 7 ppm (2H, d) 4 9 ppm (2H, s) 4 45 ppm (2H, t), 4 ppm (2H, d) 2 35 ppm (3H, s) 1 85 ppm (2H, m) 0 9 ppm (3H, t)

EXAMPLE 30

3-Methyl-5-phenyl-1-(2 2 2-trifluoroethyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = 2,2,2-trifluoroethyl, R3 = phenyl)

Step 7

According to M8, 0 8 g (3 2 mmol) of 5-methyl-4-nitro-2-(2,2,2-trifluoroethyl)-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 54 g (3 2 mmol) of 2-aminoacetophenone hydrochloride to give 0 14 g (12%) of an amide of type C (see scheme 1)

Rf (cyclohexane/EtOAc 5/5) = 0 76

MS (ES+), m/z = 371

^{1}H NMR ($CDCl_3$, 400 MHz),

8 5 ppm (1H, s) 8 0 ppm (2H, d) 7 7 ppm (1H, m) 7 55 ppm (2H, m) 5 2 ppm (2H, m) 5 0 ppm (2H, d) 2 6 ppm (3H, s)

Step 8

According to M11, 0 14 g (0 38 mmol) of the amide C (see scheme 1) is refluxed with 0 23 g of iron and 0 046 ml of 36% HCl in an ethanol/water mixture to give 0 1 g (80 5%) of the expected product D (see scheme 1)

MS (ES+) m/z = 323

^{1}H NMR ($CDCl_3$, 400 MHz),

9 0 ppm (2H, m) 7 5 ppm (3H, m) 6 6 ppm (1H, t) 5 3 ppm (2H, m) 4 2 ppm (2H, d) 2 5 ppm (3H, s)

EXAMPLE 31

5-Cyclohexyl-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl R3 = cyclohexyl)

Synthesis of the α-amino ketone

According to M6, 2 7 g (13 2 mmol) of 2-bromo-1-cyclohexylethanone (*Tetrahedron*, 48, 1, 67-78 1992) are mixed with 1 92 g (13 7 mmol) of hexamethylenetetramine in 20 ml of chloroform The mixture is heated at 48°C for 4 hours and then evaporated to dryness The residue is taken up in 20 ml of ethanol and 9 ml of 36% hydrochloric acid After leaving overnight at room temperature, the reaction medium is filtered The filtrate is evaporated to dryness to give an oil which is crystallized from diethyl ether After filtration and drying, 2 08 g (80%) of 2-amino-1-cyclohexylethanone hydrochloride are obtained in the form of a paste

MS (ES+), m/z = 141

Rf (80/20 CH_2Cl_2/MeOH) 0 31

Step 7

According to M8, 1 8 g (8 9 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) are reacted with 1 6 g (8 9 mmol) of 2-amino-1-cyclohexylethanone hydrochloride to give 1 15 g (40%) of an amide of type C (see scheme 1)

Rf (CH_2Cl_2/MeOH 95/5) = 0 48

^1H NMR ($CDCl_3$, 400 MHz),

7 6 ppm (1H, bs) 4 4 ppm (2H, d) 4 3 ppm (2H, q), 2 5 ppm (3H, s) 2 4 ppm (1H, m), 2 0 to 1 3 ppm (13H, m)

Step 8

According to M11, 0 65 g (2 mmol) of the amide C (see scheme 1) is refluxed with 1 2 g of iron and 0 2 ml of 36%

HCl in an ethanol/water mixture to give 0 35 g (64%) of the expected product D (see scheme 1)

m p 50 C

MS (ES+), m/z = 275

^{1}H NMR (C_6D_6, 400 MHz),

6 6 ppm (1H, t) 4 6 ppm (2H q) 3 6 ppm (2H, d), 2 5 ppm (1H, td) 2 4 ppm (3H, s) 1 9 to 1 3 ppm (10H, m) 1 5 ppm (3H, t)

EXAMPLE 32

1-Ethyl-3-methyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl R3 = 4-pyridyl)

Step 7

According to M8, 1 24 g (6 2 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) are reacted with 1 3 g (6 2 mmol) of 2-amino-1-pyrid-4-yl-ethanone hydrochloride (*J Med Chem*, **38**, 17, 3342-3350, 1995 *J Amer Chem Soc*, **67**, 1468-1472, 1945) to give 0 77 g (39%) of an amide of type C (see scheme 1)

Rf (80/20 CH_2Cl_2/acetone) = 0 39

^{1}H NMR (DMSO, 400 MHz),

9 4 ppm (1H, t) 8 7 ppm (2H, d) 7 8 ppm (2H, d) 4 8 ppm (2H, d) 4 1 ppm (2H q) 2 3 ppm (3H, s) 1 2 ppm (3H, t)

Step 8

According to M11, 0 76 g (2 4 mmol) of the amide C (see scheme 1) is refluxed with 1 43 g of iron and 0 24 ml of 36% HCl in an ethanol/water mixture to give 0 1 g (15%) of the expected product D (see scheme 1)

m p 148°C

MS (ES+), m/z = 270

^{1}H NMR ($CDCl_3$, 400 MHz),

8 8 ppm (2H, d) 8 3 ppm (1H, t), 7 9 ppm (2H, d) 4 4 ppm (2H, q) 4 1 ppm (2H, d) 2 3 ppm (3H, s) 1 4 ppm (3H, t)

EXAMPLE 33

5-*tert*-Butyl-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl R3 = *tert*-butyl)

Step 7

According to M8, 0 66 g (3 3 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 5 g (3 3 mmol) of 1-amino-3,3-dimethyl-butan-2-one hydrochloride (*J Org Chem*, **53**, 5, 1113-1114, 1988) to give 0 72 g (73 5%) of an amide of type C (see scheme 1)

Rf (90/10 CH_2Cl_2/MeOH) = 0 88

^1H NMR ($CDCl_3$, 400 MHz),

7 6 ppm (1H, bs) 4 5 ppm (2H, d) 4 3 ppm (2H, q) 2 6 ppm (3H, s) 1 5 ppm (3H, t) 1 3 ppm (9H, s)

Step 8

According to M11, 0 71 g (2 4 mmol) of the amide C (see scheme 1) is refluxed with 1 43 g of iron and 0 24 ml of 36% HCl in an ethanol/water mixture to give 0 27 g (46%) of the expected product D (see scheme 1)

m p 120°C

MS (ES+), m/z = 249

^1H NMR ($CDCl_3$, 400 MHz),

6 6 ppm (1H, t) 4 5 ppm (2H q) 3 7 ppm (2H, d) 2 3 ppm (3H, s) 1 4 ppm (3H, t) 1 2 ppm (9H, s)

EXAMPLE 34

3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = butyl R2 = ethyl R3 = phenyl)

Step 7

According to M8, 1 g (4 1 mmol) of 5-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 7 g (4 1 mmol) of 2-aminoacetophenone hydrochloride to give 1 25 g (86%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 359

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, d) 7 8 ppm (1H, bs) 7 7 ppm (1H, m), 7 5 ppm (2H, m) 5 0 ppm (2H, d) 4 3 ppm (2H, q) 3 0 ppm (2H, m) 1 7 ppm (2H, m) 1 5 ppm (5H, m) 1 0 ppm (3H, t)

Step 8

According to M11, 1 25 g (3 5 mmol) of the amide C (see scheme 1) are refluxed with 2 1 g of iron and 0 5 ml of 36% HCl in an ethanol/water mixture to give the expected product D (see scheme 1)

m p 105 4°C

MS (ES+), m/z = 311

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, m) 7 5 ppm (3H, m) 4 6 ppm (2H, q), 4 1 ppm (2H, d) 2 8 ppm (2H, m) 1 9 to 1 2 ppm (7H, m) 1 0 ppm (3H, t)

EXAMPLE 35

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = isopropyl R2 = ethyl R3 = tert-butyl)

Step 7

According to M9, 0 4 g (1 76 mmol) of 2-ethyl-5-isopropyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 266 g (1 76 mmol) of 1-amino-3,3-dimethylbutan-2-one hydrochloride (*J Org Chem*, 53, 5, 1113-1114, 1988) to give 0 38 g (67%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 325

Step 8

According to M12, 0 38 g (1 17 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 32 g (5 eq) of tin chloride dihydrate to give 0 22 g (68%) of the expected product D (see scheme 1)

MS (ES+), m/z = 277

^{1}H NMR (DMSO, 400 MHz),

8 2 ppm (1H, t) 4 4 ppm (2H, q) 3 6 ppm (2H, d) 3 1 ppm (1H, m) 1 3 ppm (3H, t) 1 25 ppm (6H, d) 1 2 ppm (9H, s)

EXAMPLE 36

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = isopropyl R2 = ethyl R3 = p-tolyl)

Step 7

According to M9, 0 4 g (1 76 mmol) of 2-ethyl-5-isopropyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 327 g (1 76 mmol) of 2-amino-1-*p*-tolylethanone hydrochloride to give 0 32 g (51%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 359

^{1}H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (2H, d) 7 7 ppm (1H, bs) 7 3 ppm (2H, d), 5 0 ppm (2H, d) 4 3 ppm (2H, q) 3 6 ppm (1H, m) 2 4 ppm (3H, s), 1 5 ppm (3H, t) 1 3 ppm (6H d)

Step 8

According to M12, 0 32 g (1 17 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 01 g of tin chloride dihydrate to give 0 13 g (47%) of the expected product D (see scheme 1)

MS (ES+), m/z = 311

^{1}H NMR (DMSO, 400 MHz),

8 2 ppm (1H, t) 7 9 ppm (2H, d) 7 3 ppm (2H, d), 4 4 ppm (2H, q) 4 0 ppm (2H, d) 3 2 ppm (1H, m), 2 3 ppm (3H, s) 1 3 ppm (3H, t), 1 2 ppm (6H, d)

EXAMPLE 37

4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-e][1,4]diazepin-5-yl)benzonitrile
(R1 = isopropyl R2 = ethyl R3 = 4-cyanophenyl)

Step 7

According to M9, 0 4 g (1 76 mmol) of 2-ethyl-5-isopropyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 346 g (1 76 mmol) of 4-(2-aminoethanoyl)benzonitrile hydrochloride (*Yakugaku Zasshi*, **72**, 305-307, 1952) to give 0 27 g (41%) of an amide of type C (see scheme 1)

MS (ES-), m/z = 368

^{1}H NMR ($CDCl_3$, 400 MHz),

8 1 ppm (2H, d) 7 8 ppm (2H, d) 7 75 ppm (1H, bs) 5 0 ppm (2H d) 4 3 ppm (2H, m) 3 5 ppm (1H, m) 1 5 ppm (3H, m) 1 3 ppm (6H, m)

Step 8

According to M12, 0 27 g (0 7 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 0 82 g of tin chloride dihydrate to give 0 077 g (33%) of the expected product D (see scheme 1)

MS (ES+), m/z = 322

^{1}H NMR($CDCl_3$, 400 MHz),

8 3 ppm (1H, t), 8 2 ppm (2H, m) 8 0 ppm (2H, m) 4 45 ppm (2H, q) 4 05 ppm (2H, m) 3 2 ppm (1H, m) 1 4 ppm (3H, t) 1 3 ppm (6H, d)

Example 38

1-Ethyl-3-isopropyl-5-(4-pyrrolidin-1-yl-phenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

(R1 = isopropyl R2 = ethyl R3 = 4-(1-pyrrolidyl)phenyl

Synthesis of the α-amino ketone B with R3 = 4-(1-pyrrolidinyl)phenyl

According to M6, 16 1 g (60 mmol) of 2-bromo-1-(4-(1-pyrrolidinyl)phenyl)ethanone are mixed with 8 75 g (62 4 mmol) of hexamethylenetetramine in 240 ml of chloroform The mixture is heated at 48°C for 4 hours and then filtered at room temperature The precipitate is taken up in 88 ml of ethanol and 44 ml of 36% hydrochloric acid After stirring overnight at room temperature, the reaction medium is filtered The filtrate is evaporated to dryness to give an oil which is crystallized from ethanol After filtration, washing of the precipitate with 20 ml of water and drying, 6 3 g (43%) of 2-amino-1-(4-(1-pyrrolidine)phenyl)-ethanone hydrochloride are obtained in the form of a beige powder containing 3% by weight of NH_4Cl

^1H NMR (DMSO, 400 MHz),

8 1 ppm (3H, s) 7 65 ppm (2H, d) 6 45 ppm (2H, d) 4 2 ppm (2H, m) 3 2 ppm (4H, m) 1 8 ppm (4H, t)

Step 7

According to M9, 0 4 g (1 76 mmol) of 2-ethyl-5-isopropyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 437 g (1 76 mmol) of 2-amino-1-(4-(1-pyrrolidine)phenyl)-ethanone hydrochloride (97%) to give 0 36 g (49%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 414

Step 8

According to M12, 0 36 g (0 87 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 0 98 g (5 eq) of tin chloride dihydrate to give 0 143 g (45%) of the expected product D (see scheme 1)

MS (ES+), m/z = 366

^{1}H NMR (DMSO, 400 MHz),

8 2 ppm (1H, t) 7 9 ppm (2H, d) 6 6 ppm (2H, d) 4 4 ppm (2H, q) 3 95 ppm (2H d) 3 3 ppm (4H, m) 3 2 ppm (1H, m) 2 ppm (4H, m) 1 35 ppm (3H, t) 1 3 ppm (6H, d)

EXAMPLE 39

5-(2,4-Dimethoxyphenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = isopropyl R2 = ethyl R3 = 2,4-dimethoxyphenyl)

Step 7

According to M9, 0 4 g (1 76 mmol) of 2-ethyl-5-isopropyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 408 g (1 76 mmol) of 2-amino-1-(2,4-dimethoxyphenyl)-ethanone hydrochloride to give 0 47 g (66%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 40

Step 8

According to M12, 0 47 g (1 16 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 31 g of tin chloride dihydrate to give 0 152 g (37%) of the expected product D (see scheme 1)

MS (ES+), m/z = 357

^{1}H NMR (DMSO, 400 MHz),

8 3 ppm (1H, t) 7 6 ppm (1H, d) 6 7 ppm (2H, m) 4 45 ppm (2H, q) 3 9 ppm (3H, s) 3 85 ppm (2H,d) 3 8 ppm (3H, s) 3 2 ppm (1H, m) 1 4 ppm (3H, t) 1 2 ppm (6H, d)

EXAMPLE 40

5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = isopropyl R2 = propyl R3 = *tert-butyl*)

Step 7

According to M9, 0 425 g (1 76 mmol) of 5-isopropyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 267 g (1 76 mmol) of 1-amino-3,3-dimethylbutan-2-one hydrochloride (*J Org Chem*, **53**, 5, 1113-1114, 1988) to give 0 43 g (72%) of an amide of type C (see Scheme 1)

MS (ES+), m/z = 33

Step 8

According to M12, 0 43 g (1 27 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 43 g of tin chloride dihydrate to give 0 236 g (64%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 291

^{1}H NMR (DMSO, 400 MHz),

8 25 ppm (1H, bs) 4 4 ppm (2H, bs) 3 6 ppm (2H, s) 3 2 ppm (1H, m) 1 8 ppm (2H, m) 1 3 ppm (6H d) 1 25 ppm (9H, s) 0 85 ppm (3H, t)

EXAMPLE 41

3-Isopropyl-1-propyl-5-*p*-tolyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

(R1 = isopropyl R2 = propyl, R3 = *p*-tolyl)

Step 7

According to M9, 0 425 g (1 76 mmol) of 5-isopropyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 327 g (1 76 mmol) of 2-amino-1-*p*-tolylethanone hydrochloride to give 0 37 g (57%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 373

Step 8

According to M12, 0 37 g (1 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 12 g of tin chloride dihydrate to give 0 176 g (55%) of the expected product D (see scheme 1)

MS (ES+), m/z = 325

^{1}H NMR (DMSO, 400 MHz),

8 1 ppm (1H, t), 7 7 ppm (2H, d) 7 1 ppm (2H, d), 4 25 ppm (2H, t) 3 8 ppm (2H, d) 3 1 ppm (1H m) 2 2 ppm (3H, s) 1 6 ppm (2H, m) 1 1 ppm (6H d) 0 7 ppm (3H, t)

EXAMPLE 42

4-(3-Isopropyl-8-oxo-1-propyl-1 6,7,8-tetrahydro-pyrazolo[4,3-e][1,4]diazepin-5-yl)benzonitrile

(R1 = isopropyl, R2 = propyl R3 = 4-cyanophenyl)

Step 7

According to M9, 0 425 g (1 76 mmol) of 5-isopropyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 346 g (1 76 mmol) of 4-(2-aminoethanoyl)benzonitrile hydrochloride (*Yakugaku Zasshi*, 72, 305-307, 1952) to give 0 32 g (48%) of an amide of type C (see Scheme 1)

MS (ES+), m/z = 384

^{1}H NMR ($CDCl_3$, 400 MHz),

8 1 ppm (2H d) 7 85 ppm (2H, d) 7 7 ppm (1H, bs) 0 ppm (2H, d) 4 3 ppm (2H, m) 3 6 ppm (1H, m), 1 9 ppm (2H, m) 1 3 ppm (6H, d) 0 9 ppm (3H m)

Step 8

According to M12, 0 32 g (0 834 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 0 94 g of tin chloride to give 0 076 g (27%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 336

^{1}H NMR (DMSO, 400 MHz),

8 3 ppm (1H, bs) 8 15 ppm (2H, m), 8 0 ppm (2H, m), 4 4 ppm (2H, q) 4 05 ppm (2H, m) 3 2 ppm (1H, m) 1 8 ppm (2H, m) 1 3 ppm (6H, d) 0 9 ppm (3H, t)

EXAMPLE 43

5-(2,4-Dimethoxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = isopropyl R2 = propyl R3 = 2,4-dimethoxyphenyl)

Step 7

According to M9, 0 425 g (1 76 mmol) of 5-isopropyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 407 g (1 76 mmol) of 2-amino-1-(2,4-dimethoxyphenyl)ethanone hydrochloride to give 0 54 g (73%) of an amide of type C (see Scheme 1)

MS (ES+), m/z = 41

Step 8

According to M12, 0 54 g (1 29 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 46 g (5 eq) of tin chloride dihydrate to give 0 246 g (51%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 371

^{1}H NMR (DMSO, 400 MHz),

8 3 ppm (1H, bs) 7 55 ppm (1H, m) 6 7 ppm (2H, m) 4 4 ppm (2H, t) 3 9 ppm (3H, s) 3 8 ppm (5H, m) 3 2 ppm (1H, m) 1 8 ppm (2H, m) 1 3 ppm (6H, m), 0 8 ppm (3H, m)

EXAMPLE 44

3,5-Di-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = *tert*-butyl R2 = ethyl R3 = *tert*-butyl)

Step 7

According to M9, 0 425 g (1 76 mmol) of 5-*tert*-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 267 g (1 76 mmol) of 1-amino-3,3-dimethylbutan-2-one hydrochloride to give 0 37 g (62%) of an amide of type C (see Scheme 1)

MS (ES+), m/z = 339

Step 8

According to M12, 0 37 g (1 09 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 23 g of tin chloride dihydrate to give 0 17 g (54%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 291

^{1}H NMR (DMSO, 400 MHz),

8 2 ppm (1H, t) 4 4 ppm (2H, q), 3 5 ppm (2H, d) 1 35 ppm (9H, s), 1 3 ppm (3H, t), 1 2 ppm (9H, s)

EXAMPLE 45

3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

(R1 = *tert*-butyl, R2 = ethyl R3 = *p*-tolyl)

Step 7

According to M9, 0 425 g (1 76 mmol) of 5-*tert*-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 327 g (1 76 mmol) of 2-amino-1-*p*-tolylethanone hydrochloride to give 0 39 g (60%) of an amide of type C (see Scheme 1)

MS (ES+), m/z = 373

Step 8

According to M12, 0 39 g (1 05 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 18 g of tin chloride dihydrate to give 0 181 g (53%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 325

^{1}H NMR (DMSO, 400 MHz),

8 25 ppm (1H, t) 7 9 ppm (2H, d) 7 3 ppm (2H, d) 4 4 ppm (2H, q) 4 0 ppm (2H, d) 2 35 ppm (3H, s) 1 4 ppm (9H, s) 1 35 ppm (3H, t)

EXAMPLE 46

4-(3-*tert*-Butyl-1-ethyl-8-oxo-1,6,7 8-tetrahydro-pyrazolo[4,3-e][1,4]diazepin-5-yl)benzonitrile

(R1 = *tert*-butyl R2 = ethyl R3 = 4-cyanophenyl)

Step 7

According to M9, 0 425 g (1 76 mmol) of 5-*tert*-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 346 g (1 76 mmol) of 4-(2-aminoethanoyl)benzonitrile hydrochloride (*Yakugaku Zasshi*, 72, 305-307, 1952) to give 0 33 g (49%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 384

^{1}H NMR ($CDCl_3$, 400 MHz),

8 1 ppm (2H, d) 7 8 ppm (2H, d) 5 0 ppm (2H, d) 4 3 ppm (2H, m), 1 5 to 1 4 ppm (12H, m)

Step 8

According to M12, 0 33 g (0 86 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 0 97 g of tin chloride dihydrate to give 0 091 g (32%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 336

^{1}H NMR (DMSO, 400 MHz),

8 3 ppm (1H, t), 8 2 ppm (2H, d) 8 0 ppm (2H, d), 4 45 ppm (2H, m) 4 0 ppm (2H, d) 1 4 ppm (9H, s) 1 35 ppm (3H, t)

EXAMPLE 47

3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = *tert*-butyl R2 = ethyl R3 = 2,4-dimethoxyphenyl)

Step 7

According to M9, 0 425 g (1 76 mmol) of 5-*tert*-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 407 g (1 76 mmol) of 2-amino-1-(2,4-dimethoxy-phenyl)ethanone hydrochloride (*J Chem Res Miniprint*, 7,

1581-1597, 1989) to give 0 56 g (76%) of an amide of type C (see Scheme 1)

MS (ES+), m/z = 419

Step 8

According to M12, 0 56 g (1 34 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 51 g of tin chloride dihydrate to give 0 112 g (23%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 371

^{1}H NMR (DMSO, 400 MHz),

8 2 ppm (1H, t) 7 4 ppm (1H, s) 6 5 ppm (2H, m) 4 3 ppm (2H, m), 3 75 ppm (3H, s) 3 65 ppm (5H, bs) 1 2 ppm (9H, s) 1 15 ppm (3H, t)

EXAMPLE 48

3,5-Di-*tert*-butyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = *tert*-butyl R2 = propyl R3 = *tert*-butyl)

Step 7

According to M9, 0 449 g (1 76 mmol) of 5-*tert*-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 267 g (1 76 mmol) of 1-amino-3,3-dimethylbutan-2-one hydrochloride (*J Org Chem*, 53, 5, 1113-1114, 1988) to give 0 42 g (68%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 353

Step 8

According to M12, 0 42 g (1 2 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 34 g of tin chloride dihydrate to give 0 154 g (42%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 305

^{1}H NMR (DMSO, 400 MHz),

8 2 ppm (1H, t) 4 3 ppm (2H, t) 3 55 ppm (2H, d) 1 7 ppm (2H, m) 1 4 ppm (9H, s) 1 2 ppm (9H, s) 0 8 ppm (3H, t)

EXAMPLE 49

3-*tert*-Butyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = *tert*-butyl R2 = propyl R3 = *p*-tolyl)

Step 7

According to M9, 0 449 g (1 76 mmol) of 5-*tert*-butyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 327 g (1 76 mmol) of 2-amino-1-p-tolylethanonehydrochloride to give 0 43 g (63%) of an amide of type C (see Scheme 1)

MS (ES+), m/z = 387

Step 8

According to M12, 0 43 g (1 11 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 26 g of tin chloride to give 0 163 g (43%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 339

^{1}H NMR (DMSO, 400 MHz),

8 3 ppm (1H, t) 7 9 ppm (2H, m) 7 3 ppm (2H, m) 4 4 ppm (2H, t) 4 0 ppm (2H, d) 2 4 ppm (3H, s), 1 8 ppm (2H, t) 1 4 ppm (9H, s) 0 85 ppm (3H, t)

EXAMPLE 50

4-(3-*tert*-Butyl-8-oxo-1-propyl-1,6,7,8-tetrahydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-5-yl)benzonitrile
(R1 = *tert*-butyl, R2 = propyl R3 = 4-cyanophenyl)

Step 7

According to M9, 0 449 g (1 76 mmol) of 5-*tert*-butyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 346 g (1 76 mmol) of 4-(2-aminoethanoyl)benzonitrile

hydrochloride (*Yakagaku* Zasshi, 72, 305-307, 1952) to give 0 36 g (51%) of an amide of type C (see Scheme 1)

MS (ES-), m/z = 396

Step 8

According to M12, 0 36 g (0 9 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 02 g of tin chloride to give 0 116 g (37%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 350

^{1}H NMR (DMSO, 400 MHz),

8 35 ppm (1H, t) 8 2 ppm (2H, m) 8 0 ppm (2H, m) 4 4 ppm (2H, t) 4 0 ppm (2H, d) 1 8 ppm (2H, m), 1 4 ppm (9H, s) 0 85 ppm (3H, t)

EXAMPLE 51

3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = *tert*-butyl R2 = propyl R3 = 2,4-dimethoxyphenyl)

Step 7

According to M9, 0 449 g (1 76 mmol) of 5-*tert*-butyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 407 g (1 76 mmol) of 2-amino-1-(2,4-dimethoxyphenyl)ethanone (*J Chem Res Miniprint*, 7, 1581-1597, 1989) to give 0 59 g (77%) of an amide of type C (see Scheme 1)

MS (ES+), m/z = 433

Step 8

According to M12, 0 59 g (1 36 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 54 g of tin chloride dihydrate to give 0 184 g (35%) of the expected product D (see scheme 1)

MS (ES+), m/z = 385

^{1}H NMR (DMSO, 400 MHz),

8 4ppm (1H, t) 7 55 ppm (1H, m) 6 6 ppm (2H m) 4 35 ppm (2H, q) 3 9 ppm (3H, s) 3 8 ppm (5H, m) 1 8 ppm (2H, m) 1 35 ppm (9H, s), 0 8 ppm (3H, t)

EXAMPLE 52

3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione

(R1 = butyl R2= ethyl R3 = phenyl)

Step 9

0 65g (2 mmol) of 3-butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is reacted with 1 77 g (4 mmol) of Lawesson's reagent and refluxed in toluene overnight to give 0 4 g (60%) of the desired thiolactam of type E (see Scheme 1)

Rf (95/5 CH_2Cl_2/acetone) = 0 65

m p 151 5°C

MS (ES+), m/z = 327

^{1}H NMR ($CDCl_3$, 400 MHz),

8 8 ppm (1H,t) 8 0 ppm (2H, m) 7 4 ppm (3H, m) 4 8 ppm (2H, q) 4 2 ppm (2H, d) 2 8 ppm (2H, m), 1 7 ppm (2H, m), 1 5 ppm (3H, m) 1 4 ppm (2H, m) 0 9 ppm (3H, t)

EXAMPLE 53

1-Ethyl-3-methyl-5-pyrid-3-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl R3 = 3-pyridyl)

Step 7

According to M8, 1 9 g (9 5 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) are reacted with 2 g (9 5 mmol) of 2-amino-1-pyrid-3-ylethanone hydrochloride (*Chem Pharm Bull* , **32**, 7, 2536-2543, 1984 *J Amer Chem Soc* , **67**, 1468-1472, 1945) to give 2 2 g (73%) of an amide of type C (see Scheme 1)

Rf (90/10 CH_2Cl_2/acetone) = 0 27

^1H NMR ($CDCl_3$, 400 MHz),

9 55 ppm (1H t) 9 2 ppm (1H, s) 8 8 ppm (1H, d) 7 95 ppm (2H, m) 5 0 ppm (2H, d) 4 2 ppm (2H, q), 2 4 ppm (3H, s) 1 4 ppm (3H, t)

Step 8

According to M12 1 1 g (3 47 mmol) of the amide C (see scheme 1) are refluxed in ethanol with 3 9 g (5 eq) of tin chloride dihydrate to give 0 26 g (28%) of the expected product D (see scheme 1)

m p = 178°C

MS (ES+), m/z = 270

^1H NMR (DMSO, 400 MHz),

9 2 ppm (1H, s) 8 7 ppm (1H, d) 8 4 ppm (1H, d) 8 3 ppm (1H, t) 7 5 ppm (1H, dd) 4 4 ppm (2H, q), 4 1 ppm (2H, d) 2 3 ppm (3H, s), 1 4 ppm (3H, t)

EXAMPLE 54

1-Ethyl-3-methyl-5-pyrid-2-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl, R2 = ethyl R3 = 2-pyridyl)

Step 7

According to M8, 1 9 g (9 5 mmol) of 2-ethyl-5-methyl-4-nitro-2H-pyrazole-3-carboxylic acid (A) are reacted with 2 g (9 5 mmol) of 2-amino-1-pyrid-2-ylethanone hydrochloride (*J Amer Chem Soc* , 67, 1468-1472, 1945 *J Chem Soc* , 753, 1938) to give 2 2 g (73%) of an amide of type C (see Scheme 1)

Rf (90/10 CH_2Cl_2/acetone) = 0 38

MS (ES+), m/z = 318

^1H NMR ($CDCl_3$, 400 MHz),

396

9 5 ppm (1H bs) 8 8 ppm (1H, m) 8 0 ppm (2H, m) 7 7 ppm (1H, m) 5 0 ppm (2H, d) 4 2 ppm (2H q), 2 4 ppm (3H, s) 1 4 ppm (3H, t)

Step 8

According to M12, 1 1 g (3 47 mmol) of the amide C (see scheme 1) are refluxed in ethanol with 3 9 g (5 eq) of tin chloride dihydrate to give 0 19 g (20%) of the expected product D (see Scheme 1)

m p = 153°C

MS (ES+), m/z = 270

^{1}H NMR (DMSO, 400 MHz),

8 7 ppm (H, d) 8 3 ppm (21H, m) 8 0 ppm (1H, t), 7 5 ppm (1H, dd) 4 5 ppm (2H, q) 4 4 ppm (2H, d) 2 3 (3H, s) 1 4 ppm (3H, t)

EXAMPLE 55

1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-ylidenecyanamide

(R1 = methyl R2 = ethyl R3 = phenyl)

Step 10

According to M13, 2 g (7 mmol) of 1-ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione are reacted with 0 21 g of 80% sodium hydride in refluxing THF for 1 h, followed by addition of 0 52 ml of methyl iodide, at room temperature The mixture is refluxed for 2 h to give 2 1 g (100%) of the expected methylsulphanyl G (see scheme 1)

MS (ES+), m/z = 299

^{1}H NMR ($CDCl_3$, 400 MHz),

8 1 ppm (2H, d) 7 5 ppm (3H, m) 4 5 ppm (4H, m), 2 5 ppm (3H, s) 2 4 ppm (3H, s) 1 5 ppm (3H, t)

Step 11

0 5 g (1 67 mmol) of the methylsulphanyl G is reacted with 0 14 g (2 eq) of cyanamide to give 0 29 g (60%) of the desired product F (see scheme 1)

Rf (95/5 CH_2Cl_2/MeOH) = 0 32

m p = 280°C

MS (ES+), m/z = 293

^1H NMR (DMSO, 400 MHz),

9 5 ppm (1H, s), 8 2 ppm (2H, m) 7 5 ppm (3H, m) 4 5 ppm (2H, q) 4 2 ppm (2H, s) 2 3 ppm (3H, s) 1 4 ppm (3H, t)

EXAMPLE 56

N-[4-(1-Ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-e][1,4]diazepin-5-yl)phenyl]-(phenylsulphonyl)benzenesulphonamide,

(R1 = methyl, R2 = ethyl R3 = 4-N-(phenylsulphonyl)-benzenesulphonamidephenyl)

0 2 g (0 7 mmol) of 5-(4-aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one, is introduced into a round-bottomed flask and 10 ml of acetonitrile are added, followed by 0 158 g (1 41 mmol) of 1,4-diazabicyclo[2 2 2]octane, and 0 116 ml (0 91 mmol) of benzenesulphonyl chloride The reaction mixture is stirred overnight at room temperature and then evaporated to dryness to give 0 54 g of an oily compound The crude product is purified by flash chromatography using the following elution gradient from CH_2Cl_2 to 98/2 CH_2Cl_2/methanol After evaporation and crystallization from methanol, 0 19 g (48%) of a yellow powder are obtained

MS (ES+), m/z = 564

m p = >230°C

^1H NMR ($CDCl_3$, 400 MHz),

1 5 ppm (3H, t) 2 4 ppm (3H s) 4 1 ppm (2H, m) 4 55 ppm (2H, q) 6 25 ppm (1H, m) 7 1 ppm (2H, m) 7 6 ppm (4H, m) 7 7 ppm (2H, m) 7 85 ppm (6H, m)

EXAMPLE 57

3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-ylidene-cyanamide

(R1 = *tert*-butyl R2 = ethyl R3 = phenyl)

Step 10

According to M13, 1 65 g (5 05 mmol) of 3-*tert*-butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione are reacted with 0 15 g of 80% sodium hydride in refluxing THF for 1 hour, followed by addition of 0 38 ml of methyl iodide, at room temperature The mixture is refluxed for 2 h to give 1 55 g (90%) of the expected methylsulphanyl G (see scheme 1)

Step 11

0 5 g (1 47 mmol) of the methylsulphanyl G is reacted with 0 12 g (2 eq) of cyanamide to give 0 185 g (38%) of the expected product of type F (see Scheme 1)

Rf (95/5 CH_2Cl_2/methanol) = 0 57

m p = 250°C

MS (ES+), m/z = 335

^1H NMR (DMSO, 400 MHz),

9 5 ppm (1H s) 8 1 ppm (2H, d), 7 5 ppm (3H, d) 4 5 ppm (2H, q) 4 2 ppm (2H, bs) 1 4 ppm (6H, s) 1 35 ppm (3H, m)

EXAMPLE 58

1-Cyclopropylmethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

(R1 = methyl R2 = cyclopropylmethyl R3 = phenyl)

Step 5

According to M5, 1 9 g (9 5 mmol) of ethyl-3-methyl-4-nitro-1*H*-5-pyrazolecarboxylate (commercial) are reacted with 5 g (37 mmol) of (bromomethyl)cyclopropane (commercial) in the presence of 1 43 g (9 5 mmol) of sodium iodide to give 1 14 g (48%) of a pyrazole A5 (see scheme 1)

Rf (80/20 cyclohexane/EtOAc) = 0 47

^{1}H NMR ($CDCl_3$, 400 MHz),

4 45 ppm (2H, q) 4 05 ppm (2H, d) 2 5 ppm (3H, s), 1 4 ppm (3H, t) 1 3 ppm (1H m) 0 6 ppm (2H, m), 0 4 ppm (2H, m)

Step 6

1 14 g (4 5 mmol) of the pyrazole A5 (see scheme 1) are reacted with 0 27 g (6 75 mmol) of sodium hydroxide in a mixture of methanol and water to give 0 93 g (91%) of a pyrazole of type A (see Scheme 1)

MS (ES-), m/z = 224

Step 7

According to M9, 0 5 g (2 22 mmol) of 2-(cyclopropylmethyl)-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 38 g (2 22 mmol) of 2-aminoacetophenone hydrochloride to give 1 g of the compound C (see Scheme 1)

MS (ES+), m/z = 343

Step 8

According to M12, 1 g (2 9 mmol) of compound C (see scheme 1) is refluxed in ethanol with 2 5 g (11 mmol), of tin chloride dihydrate to give 0 17 g (27%) of the expected product D (see scheme 1)

Rf (90/10 CH_2Cl_2/acetone) = 0 42

MS (ES+), m/z = 295

^{1}H NMR ($CDCl_3$, 400 MHz)

400

7 95 ppm (2H, m) 7 5 ppm (3H, m) 6 15 ppm (1H t)
4 4 ppm (2H, d) 4 1 ppm (2H, d) 2 45 ppm (3H, s)
1 45 ppm (1H, m) 0 5 ppm (2H m) 0 45 ppm (2H, m)

EXAMPLE 59

1-Allyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = methyl R2 = allyl R3 = phenyl)

Step 5

According to M5, 2 5 g (12 5 mmol) of ethyl-3-methyl-4-nitro-1*H*-5-pyrazolecarboxylate (commercial) are reacted with 1 09 ml (12 5 mmol) of allyl bromide (commercial) in the presence of 0 38 g (12 5 mmol) of 80% sodium hydride in 1,2-dimethoxyethane to give 0 35 g (12%) of a pyrazole A5 (see Scheme 1)

Rf (70/30 cyclohexane/EtOAc) = 0 53

^{1}H NMR ($CDCl_3$, 400 MHz),

5 9-6 ppm (1H, m) 5 3 ppm (1H, d) 5 2 ppm (1H, d)
4 8 ppm (2H, d) 4 45 ppm (2H, q) 2 5 ppm (3H, s) 1 4 ppm (3H, t)

Step 6

0 35 g (1 46 mmol) of the pyrazole A5 (see scheme 1) is reacted with 0 09 g (2 25 mmol) of sodium hydroxide in a mixture of methanol and water, to give 0 071 g (23%) of a pyrazole of type A (see Scheme 1)

MS (ES^-), m/z = 210

Step 7

According to M9, 0 071 g (0 34 mmol) of 2-allyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 058 g (0 34 mmol) of 2-aminoacetophenone hydrochloride to give 0 174 g of compound C (see Scheme 1)

Step 8

401

According to M12, 0 174 g (0 5 mmol) of compound C (see scheme 1) is refluxed in ethanol with 0 38 g (1 68 mmol) of tin chloride dihydrate to give 0 01 g (11%) of the expected product D (see Scheme 1)

Rf (90/10 CH_2Cl_2/acetone) = 0 30

MS (ES+) m/z = 281

EXAMPLE 60

1-Ethyl-3-methyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl R3 = 4-trifluoromethylphenyl)

Step 7

According to M9, 0 33 g (1 67 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 4 g (1 67 mmol) of 2-amino-1-(4-trifluoromethylphenyl)ethanone hydrochloride (*J Amer Chem Soc*, **75**, 5884-5886, 1953 *J Org Chem*, **42**, 5, 868-871, 1977) to give a crude amide of type C (see scheme 1)

MS (ES-), m/z = 383

Step 8

According to M12, 0 64 g (1 67 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 9 g (5 eq) of tin chloride dihydrate to give 0 153 g (27%) of the expected product of type D (see Scheme 1)

Rf (90/10 CH_2Cl_2/acetone) = 0 22

m p = 195°C

MS (ES+), m/z = 337

^1H NMR (DMSO, 400 MHz),

8 4 ppm (1H, t) 8 3 ppm (2H, d) 8 0 ppm (2H, d) 4 5 ppm (2H, q) 4 1 ppm (2H, d) 2 4 ppm (3H, s) 1 4 ppm (3H, t)

EXAMPLE 61

1-Ethyl-3-isopropyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = isopropyl R2 = ethyl R3 = 4-trifluoromethylphenyl)

Step 7

According to M9, 0 38 g (1 67 mmol) of 2-ethyl-5-isopropyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 4 g (1 67 mmol) of 2-amino-1-(4-trifluoromethylphenyl)-ethanone hydrochloride (*J Amer Chem Soc*, **75**, 5884-5886, 1953, *J Org Chem*, **42**, 5, 868-871, 1977) to give a crude amide of type C (see Scheme 1)

MS (ES-), m/z = 411

Step 8

According to M12, 0 69 g (1 67 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 9 g (5 eq) of tin chloride dihydrate to give 0 161 g (26 5%) of the expected product D (see Scheme 1)

Rf (90/10 CH_2Cl_2/acetone) = 0 28

m p = 133

MS (ES+), m/z = 364

^1H NMR (DMSO, 400 MHz),

8 3 ppm (1H, t) 8 2 ppm (2H, d) 7 9 ppm (2H, d) 4 4 ppm (2H, q) 4 0 ppm (2H, d) 3 3 ppm (1H, m) 1 4 to 1 3 ppm (9H, m)

EXAMPLE 62

1-Ethyl-3-methyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = *tert*-butyl, R2 = ethyl R3 = 4-trifluoromethylphenyl)

Step 7

According to M9, 0 4 g (1 67 mmol) of 5-*tert*-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 4 g (1 67 mmol) of 2-amino-1-(4-trifluoromethylphenyl)-ethanone hydrochloride (*J Amer Chem Soc*, **75**, 5884-5886,

1953 *J Org Chem*, **42**, 5, 868-871, 1977) to give a crude amide of type C (see Scheme 1)

MS (ES-), m/z = 425

Step 8

According to M12, 0 712 g (1 67 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 1 9 g (5 eq) of tin chloride dihydrate to give 0 14 g (22%) of the expected product D (see Scheme 1)

Rf (90/10 CH_2Cl_2/acetone) = 0 33

m p = 144°C

MS (ES+), m/z = 379

^1H NMR (DMSO, 400 MHz)

8 3 ppm (1H, t) 8 2 ppm (2H, d) 7 9 ppm (2H, d) 4 4 ppm (2H, q) 4 1 ppm (2H, d) 1 4 ppm (9H, s) 1 35 ppm (3H, t)

EXAMPLE 63

3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione

(R1 = isopropyl R2 = propyl R3 = *p*-tolyl)

Step 9

0 9 g (2 7 mmol) of 3-isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is reacted with 2 24 g (5 53 mmol) of Lawesson's reagent and refluxed in toluene overnight to give 0 73 g (77%) of the thiolactam of type E (see scheme 1)

Rf (CH_2Cl_2) = 0 22

m p = 162 9°C

MS (ES+), m/z = 340 9

^1H NMR ($CDCl_3$, 400 MHz)

0 9 ppm (3H, t), 1 35 ppm (6H, m), 1 9 ppm (2H, m), 2 4 ppm (3H, s) 3 3 ppm (1H, m) 4 15 ppm (2H, m), 4 75 ppm (2H, m) 7 2 ppm (2H, d) 7 9 ppm (2H, d) 8 65 ppm (1H, m)

EXAMPLE 64

3,5-Di-*tert*-butyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione

(R1 = *tert*-butyl R2 = propyl R3 = *tert*-butyl)

Step 9

1 5 g (4 9 mmol) of 3,5-di-*tert*-butyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one are reacted with 4 g (9 8 mmol) of Lawesson's reagent and refluxed in toluene overnight to give 1 4 g (90%) of the thiolactam of type E (see Scheme 1)

Rf (80/20 cyclohexane/EtOAc) = 0 54

m p 205°C

MS (ES+), m/z = 321

^{1}H NMR ($CDCl_3$, 400 MHz)

9 0 ppm (1H, m) 4 7 ppm (2H, m) 1 9 ppm (2H, m) 1 4 ppm (9H, s) 1 25 ppm (9H, s) 0 9 ppm (3H, t)

EXAMPLE 65

5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione

(R1 = isopropyl R2 = propyl R3 = *tert*-butyl)

Step 9

0 35 g (1 2 mmol) of 5-*tert*-butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one is reacted with 0 98 g (2 4 mmol) of Lawesson's reagent and refluxed in toluene overnight to give 0 25 g (68%) of the thiolactam of type E (see Scheme 1)

Rf (70/30 cyclohexane/EtOAc) = 0 67

m p 165°C

MS (ES+), m/z = 307

^{1}H NMR ($CDCl_3$, 400 MHz),

8 8 ppm (1H, m) 4 7 ppm (2H, m) 3 75 ppm (2H, m) 3 2 ppm (1H, m) 1 9 ppm (2H, m) 1 3 ppm (6H, d), 1 25 ppm (9H, s), 0 9 ppm (3H,t)

EXAMPLE 66

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione

(R1 = isopropyl R2 = ethyl R3 = *p*-tolyl)

Step 9

0 62 g (2 mmol) of 1-ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is reacted with 1 62 g (4 mmol) of Lawesson's reagent and refluxed in toluene overnight to give 0 567 g (87%) of the desired thiolactam of type E (see Scheme 1)

Rf (98/2 CH_2Cl_2/MeOH) = 0 46

m p 178 C

MS (ES+), m/z = 327

^1H NMR ($CDCl_3$, 400 MHz),

8 5 ppm (1H, bs), 7 8 ppm (2H, d), 7 15 ppm (2H, d), 4 75 ppm (2H, q) 4 1 ppm (2H, bs) 3 2 ppm (1H, m) 2 3 ppm (3H, s) 1 4 ppm (3H t) 1 3 ppm (6H, d)

EXAMPLE 67

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione

(R1 = isopropyl R2 = ethyl R3 = *tert*-butyl)

Step 9

0 4 g (1 45 mmol) of 5-*tert*-butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is reacted with 1 17 g (2 9 mmol) of Lawesson's reagent and refluxed in toluene overnight to give 0 193 g (46%) of the desired thiolactam of type E (see Scheme 1)

Rf (98/2 CH_2Cl_2/MeOH) = 0 43

406

m p 218°C

MS (ES+), m/z = 293

^{1}H NMR (DMSO, 400 MHz),

10 35 ppm (1H, bs) 4 65 ppm (2H, q) 3 9-3 3 ppm (2H, bs) 3 1 ppm (1H, m) 1 3 ppm (3H, t) 1 2 ppm (6H, d) 1 15 ppm (9H, s)

EXAMPLE 68

(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = *sec*-butyl R2 = ethyl R3 = phenyl)

Synthesis of the pyrazole (following steps 1, 2, 3, 5 and 6)

Step 1

3 44 g (149 8 mmol) of sodium are dissolved portionwise in 200 ml of anhydrous ethanol under nitrogen, at room temperature 20 35 ml (149 8 mmol) of diethyl oxalate in 60 ml of anhydrous ethanol are added 15 g (149 8 mmol) of 3-methyl-2-pentanone are added The reaction mixture is refluxed for 3 h, under nitrogen and with stirring, and is then evaporated to dryness the residue is taken up in 300 ml of HCl (1 2N) and then extracted with diethyl ether (3 times 200 ml) The organic phase is dried over sodium sulphate and then concentrated to give 26 1 g (89%) of a colourless oil (compound A1, see scheme 1)

Rf (60/40 CH_2Cl_2/heptane) = 0 4

^{1}H NMR ($CDCl_3$, 400 MHz),

0 9 ppm (3H, t), 1 1 ppm (3H, d) 1 4 ppm (3H, t) 1 5 ppm (1H, m), 1 7 ppm (1H, m), 2 4 ppm (2H, m) 4 3 ppm (2H, q), 6 4 ppm (1H, s), 14 6 ppm (1H, m)

Step 2

8 25 g (125 mmol) of potassium hydroxide are dissolved in 120 ml of water and the reaction medium is cooled to 0°C

25 g (125 mmol) of compound A1 (see scheme 1) are added portionwise and the mixture is stirred for 15 min at 0°C 16 3 g (130 11 mmol) of hydrazine sulphate are added and the mixture is then stirred for 20 min at 0°C It is stirred at room temperature overnight, after which 200 ml of water are added and the mixture is extracted with dichloromethane (3 x 200 ml) The organic phase obtained is washed with saturated NaCl solution (1 x 200 ml) and then dried over sodium sulphate and concentrated 24 5 g of an powder are obtained

The product is purified by flash chromatography (95/5 CH_2Cl_2/acetone) to give 17 6 g (68%) of a white powder (compound A6, see scheme 1)

Rf (95/5 CH_2Cl_2/acetone) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

0 85 ppm (3H, t) 1 3 ppm (3H, d) 1 35 ppm (3H, t) 1 6 ppm (1H, m) 2 8 ppm (1H, m) 4 4 ppm (2H, m) 6 6 ppm (1H, s) 11 6 ppm (1H, m)

Step 3

According to M3, 20 7 g (89 95 mmol) of copper(II) nitrate hemipentahydrate (2 5 H_2O) and 100 ml of trifluoroacetic anhydride are introduced into a round-bottomed flask, the mixture is stirred under nitrogen for 5 min and 17 g of compound A6 (see scheme 1) (80 87 mmol) dissolved in 100 ml of chloroform are then added This mixture is refluxed with stirring and under nitrogen for 5 hours This product is purified by flash chromatography (98/2 CH_2Cl_2/acetone) to give 20 g of a blueish oil This product is taken up in 200 ml of HCl (10%) and then extracted with diethyl ether (3 times 300 ml), and the organic phase is dried and concentrated to give 16 81 g (70%) of a colourless oil (compound A7, see scheme 1)

MS (ES-), m/z = 239 91

Rf (97/3 CH_2Cl_2/acetone) = 0 3

^1H NMR ($CDCl_3$ 400 MHz),

0 9 ppm (3H, t) 1 4 ppm (6H, m) 1 7 ppm (2H, m) 3 4 ppm (1H, m) 4 4 ppm (2H, q) 11 6 ppm (1H, m)

Step 5

According to M4, 0 92 g (3 81 mmol) of compound A7 (see scheme 1) and 0 5 ml (3 81 mmol) of diethyl sulphate are introduced into a round-bottomed flask and the mixture is then refluxed with stirring and under nitrogen for 1 h 30 min After cooling to room temperature, 6 g of ice and 15 ml of HCl (10%) are added and the mixture is stirred and then extracted with dichloromethane (3 times 40 ml) The organic phase is dried and concentrated to give 1 1 g of a colourless oil This product is purified by flash chromatography (gradient 9/1 to 7/3 cyclohexane/ ethyl acetate) to give 0 8 g (78%) of a white powder (compound A5, see scheme 1)

Rf (80/20 cyclohexane/ethyl acetate) = 0 3

^1H NMR ($CDCl_3$ 400 MHz),

0 9 ppm (3H, t) 1 35 ppm (3H, m) 1 45 ppm (6H, m), 1 6 ppm (1H, m) 1 8 ppm (1H, m), 3 3 ppm (1H, m), 4 25 ppm (2H, q) 4 5 ppm (2H, q)

Step 6

8 3 g (33 80 mmol) of compound A5 (see scheme 1) are dissolved in 40 ml of methanol, followed by addition of a solution of 2 g (50 7 mmol) of sodium hydroxide in 40 ml of water The mixture is stirred at RT for 2 h After evaporating off the methanol, the residue is taken up in CH_2Cl_2, an identical volume of water is added, followed by addition of concentrated (36%) hydrochloric acid to acidic pH, with stirring The organic phase is dried over Na_2SO_4 and concentrated to give 7 5 g (98%) of a white powder (compound A, see scheme 1)

^{1}H NMR ($CDCl_3$, 400 MHz),

0 9 ppm (3H, m) 1 3 ppm (3H, m) 1 5 ppm (3H, m), 1 6 ppm (1H, m) 1 8 ppm (1H, m) 3 3 ppm (1H, m), 4 5 ppm (2H, q), 9 3 ppm (1H, m)

Step 7

According to M9, 0 434 g (1 8 mmol) of 5-*sec*-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 309 g (1 8 mmol) of 2-aminoacetophenone hydrochloride to give a crude amide of type C (see Scheme 1)

MS (ES+), m/z = 359

Step 8

According to M12, 0 65 g (1 8 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 25 g (5 eq) of tin chloride dihydrate to give 0 14 g (25%) of the expected product D (see scheme 1)

MS (ES+), m/z = 311

^{1}H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (2H, m) 7 4 ppm (3H, m) 7 2 ppm (1H, m) 4 5 ppm (2H, q) 4 1 ppm (2H, t), 3 1 ppm (1H, m) 1 8 ppm (1H, m) 1 7 ppm (1H, m), 1 4 ppm (3H, t) 1 3 ppm (3H, d) 0 8 ppm (3H, t)

EXAMPLE 69

(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = *sec*-butyl R2 = ethyl, R3 = 4-pyridyl)

Synthesis of the pyrazole see steps 1, 2, 3, 5 and 6 of example 68

Step 7

According to M9, 0 434 g (1 8 mmol) of 5-*sec*-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 376 g (1 8 mmol) of 2-amino-1-pyrid-4-ylethanone

hydrchloride (*J Med Chem*, 38, 17, 3342-3350, 1995 *J Amer Chem Soc*, 67, 1468-1472, 1945) to give a crude amide of type C (see scheme 1)

MS (ES+), m/z = 359 8

Step 8

According to M12, 0 65 g (1 8 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 25 g (5 eq) of tin chloride dihdyrate to give 0 135 g (24%) of the expected product D (see scheme 1)

m p 86-88 5°C

MS (ES+), m/z = 312

^{1}H NMR ($CDCl_3$, 400 MHz),

8 8 ppm (2H, d) 7 8 ppm (2H, d) - 7 2 ppm (1H, m) 4 6 ppm (2H, q) 4 1 ppm (2H, d) 3 1 ppm (1H, m) 1 9 ppm (1H, m), 1 7 ppm (1H, m) 1 5 ppm (3H, t) 1 4 ppm (3H, d) 0 9 ppm (3H, q)

EXAMPLE 70

(±)3-*sec*-Butyl-5-phenyl-1-propyl-6,7-dihydro-*1H*-pyrazolo-[4,3-e][1,4]diazepin-8-one

(R1 = *sec*-butyl R2 = propyl R3 = phenyl)

Synthesis of the pyrazole see steps 1, 2 and 3 of example 68 and the following steps 5 and 6

Step 5

According to M5, 4 90 g (66 32 mmol) of Li_2CO_3 are added, under a stream of nitrogen, to a solution of 6 4 g (26 53 mmol) of compound A7 (see scheme 1) in 110 ml of anhydrous DMF, followed by addition of 6 5 ml (66 32 mmol) of iodopropane The reaction medium is heated at 60°C for 24 h It is cooled to room temperature and then poured into 100 ml of HCl (1 2N), the exothermicity being controlled by an ice bath After extracting with dichloromethane (3 times 100 ml), the organic phase obtained is washed with

saturated NaCl solution (100 ml), dried over Na_2SO_4 and evaporated to dryness to give 7 g of an oily compound The product is purified by flash chromatography (gradient 70/30 to 60/40 heptane/CH_2Cl_2) to give 5 g (66%) of a colourless oil which crystallizes (compound A5, see scheme 1)

Rf (50/50 heptane/CH_2Cl_2) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

0 90 ppm (6H, m) 1 25 ppm (3H, m) 1 40 ppm (3H, m) 1 60 ppm (1H m) 1 80 ppm (3H, m) 3 30 ppm (1H, m) 4 25 ppm (2H, q) 4 40 ppm (2H, q)

Step 6

4 94 g (18 41 mmol) of compound A5 (see scheme 1) are dissolved in 21 ml of methanol, followed by addition of a solution of 1 1 g (27 61 mmol) of sodium hydroxide in 21 ml of water This mixture is stirred at RT for 2 h After evaporating off the methanol, the residue is taken up in CH_2Cl_2 and an identical volume of water is added, followed by addition of concentrated (36%) hydrochloric acid to acidic pH, with stirring The organic phase is dried over Na_2SO_4 and concentrated to give 4 5 g (96%) of a white powder (compound A, see scheme 1)

^1H NMR ($CDCl_3$, 400 MHz),

0 9 ppm (6H, m) 1 3 ppm (3H, d) 1 6 ppm (1H, m) 1 8 ppm (1H, m) 1 9 ppm (2H, m) 3 3 ppm (1H, m) 4 4 ppm (2H, q) 7 6 ppm (1H, m)

Step 7

According to M9, 0 46 g (1 8 mmol) of 5-*sec*-butyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 31 g (1 8 mmol) of 2-aminoacetophenone hydrochloride to give a crude amide of type C (see scheme 1)

MS (ES+), m/z = 373

Step 8

412

According to M12, 0 67 g (1 8 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 35 g (5 eq) of tin chloride dihydrate to give 0 035 g (6%) of the expected product D (see scheme 1)

MS (ES+) m/z = 325

^{1}H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (2H, m) 7 5 ppm (3H m), 6 7 ppm (1H, m) 4 5 ppm (2H, m) 4 1 ppm (2H, m) 3 1 ppm (1H, m) 2 0 ppm to 1 6 ppm (4H, m), 1 4 ppm (3H, d) 0 9 ppm (6H, m)

EXAMPLE 71

(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = *sec*-butyl R2 = propyl R3 = 4-pyridyl)

Synthesis of the pyrazole see steps 1, 2, 3, 5, 6 of exemple 70

Step 7

According to M9, 0 46 g (1 8 mmol) of 5-*sec*-butyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid is reacted with 0 376 g (1 8 mmol) of 2-amino-1-pyrid-4-ylethanone hydrochloride (*J Med Chem* , 38, 17, 3342-3350, 1995, *J Amer Chem Soc* 67 1468-1472, 1945) to give a crude amide of type C (see scheme 1)

MS (ES+), m/z = 373 6

Step 8

According to M12, 0 62 g (1 66 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 36 g (5 eq) of tin chloride dihydrate to give 0 1 g (17 3%) of the expected product D (see scheme 1)

m p 110°C

MS (ES+), m/z = 325 8

^{1}H NMR ($CDCl_3$, 400 MHz),

8 7 ppm (2H d) 7 7 ppm (2H, d), 7 0 ppm (1H, t), 4 5 ppm (2H, q) 4 0 ppm (2H, d) 3 1 ppm (1H, m) 1 9 ppm (2H, m) 1 8 ppm (1H, m) 1 7 ppm (1H, m) 1 3 ppm (3H, d) 0 9 ppm (3H, m) 0 8 ppm (3H, m)

EXAMPLE 72

3-Cyclohexyl-1-ethyl-5-phenyl-6,7-dihydro-*1H*-pyrazolo-[4,3-e][1,4]diazepin-8-one

(R1 = cyclohexyl R2 = ethyl R3 = phenyl)

Synthesis of the pyrazole see the following steps 1, 2, 3, 5 and 6

Step 1

2 46 g (107 mmol) of sodium are dissolved portionwise in 250 ml of anhydrous ethanol under nitrogen at room temperature 14 52 ml (107 mmol) of diethyl oxalate in 60 ml of anhydrous ethanol are added 15 g (107 mmol) of acetylcyclohexane are added The reaction mixture is refluxed for 3 h, under nitrogen and with stirring, and then evaporated to dryness, the residue is taken up in 300 ml of HCl (1 2 N) and is then extracted with diethyl ether (3 times 200 ml) The organic phase is dried over sodium sulphate and then concentrated to give 23 2 g (96%) of a colourless oil (compound A1, see scheme 1)

Rf (60/40 CH_2Cl /n-heptane) = 0 1

^1H NMR ($CDCl_3$, 400 MHz),

1 3 ppm (8H, m) 1 8 ppm (5H, m) 2 35 ppm(1H, m) 4 3 ppm (2H, q) 6 4 ppm (1H, s) 14 6 ppm (1H, m)

Step 2

7 g (104 mmol) of potassium hydroxide are dissolved in 110 ml of water and the reaction medium is cooled to 0°C 25 g (110 mmol) of compound A1 (see scheme 1) are added portionwise and the mixture is stirred for 15 min at 0°C 13 5 g (104 mmol) of hydrazine sulphate are added and the

mixture is then stirred for 20 min at 0°C The resulting mixture is stirred overnight, 200 ml of water are then added and this mixture is extracted with dichloromethane (3 times 200 ml) The organic phase obtained is washed with saturated NaCl solution (1 x 200 ml) and then dried over sodium sulphate and concentrated 23 4 g of a powder are obtained

The product is purified by flash chromatography (gradient 97/3 to 90/10 CH_2Cl_2/acetone) to give 15 g (61%) of a white powder (compound A6, see scheme 1)

Rf (95/5 CH_2Cl_2/acetone) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

1 35 ppm (8H, m) 1 7 ppm (3H, m) 1 95 ppm (2H, m), 2 7 ppm (1H, m) 4 3 ppm (2H, q) 6 6 ppm (1H, s) 11 8 ppm (1H, m)

Step 3

According to M3, 12 77 g (54 93 mmol) of copper(II) nitrate hemipentahydrate (2 5 H_2O) and 100 ml of trifluoroacetic anhydride are introduced into a round-bottomed flask, the mixture is stirred under nitrogen for 5 min and 11 1 g of compound A6 (see scheme 1) (49 93 mmol) dissolved in 100 ml of chloroform are then added This mixture is refluxed, with stirring and under nitrogen, for 5 hours After evaporation to dryness, 18 6 g of a blueish oil are obtained This product is taken up in 200 ml of HCl (10%) and then extracted with ether (3 times 300 ml) and the organic phase is dried and concentrated to give 16 1 g of a colourless oil This product is purified by flash chromatography (98/2 CH_2Cl_2/acetone) to give 7 1 g (53%) of a white powder (compound A7, see scheme 1)

Rf (97/3 CH_2Cl_2/acetone) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

EJEMPLO 27

5-(4-Aminofenil)-1-etil-3-isopropil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = isopropilo, R_2 = etilo, R_3 = 4-aminofenilo)

Paso 7

De acuerdo con M8, 1,3 g (4,9 mmol) de ácido 2-etil-5-isopropil-4-nitro-2H-pirazol-3-carboxílico reacciona con 1,23 g de clorhidrato de 2-amino-4'-nitro-acetofenona para dar 2 g (90%) de una amida del tipo C (ver el esquema 1)

MS (ES-), m/z = 388

^{1}H NMR ($CDCl_3$, 400 MHz)

1,3 ppm (9H, s), 1,5 ppm (3H, t), 3,55 ppm (1H, q), 4,3 ppm (2H, q), 5 ppm (2H, d), 7,8 ppm (1H, m), 8,15 ppm (2H, d), 8,4 ppm (2H, d)

Paso 8

De acuerdo con M11, 2 g (5,1 mmol) de la amida C (ver el esquema 1) se refluye con 0,5 ml de HCl y 3,07 g de hierro en una mezcla de etanol/agua para dar 0,5 g (31%) del producto D esperado (ver el esquema 1)

MS (ES+), m/z = 312

punto de fusión 191°C

^{1}H NMR ($CDCl_3$, 400 MHz)

1,15 ppm (6H, m), 1,25 ppm (3H, m) 3,05 ppm (1H, q), 3,8 ppm (2H, d), 4,3 ppm (2H, q), 5,65 ppm (2H, m), 6,5 ppm (2H, d), 7,6 ppm (2H, d), 8 ppm (1H, m)

EJEMPLO 28

1-Etil-5-(4-hiroxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona

(R_1 = metilo, R_2 = etilo R_3 = 4-hidroxifenilo)

17 ml de una solución molar de BBr_3 en diclorometano se agregan gota a gota a una solución de 0,2 g de 1-etil-5-(4-metoxifenil)-3-metil-6,7-dihidro-1H-pirazolo[4,3-e][1,4]diazepin-8-ona en 84 ml de diclorometano La mezcla resultante se refluye durante 6 horas Después de enfriar a temperatura ambiente, el medio de reacción se neutraliza con una solución de bicarbonato de sodio La fase orgánica se seca y se evapora El producto se purifica mediante cromatografía rápida (gradiente CH_2Cl_2, 90/10 de CH_2Cl_2/acetona, 80/20 de CH_2Cl_2/acetona) La evaporación del solvente da 0,103 g del compuesto D en la forma de un polvo beige (54%)

Rf (90/10 de CH_2Cl_2/MeOH) = 0,25

^1H NMR (DMSO, 400 MHz)

9,5 ppm (1H, OH), 7,9 ppm (2H, m), 7,8 ppm (1H, bs), 6,9 ppm (2H, m), 4,5 ppm (2H, q), 4 ppm (2H, d), 2,4 ppm (3H, s), 1,5 ppm (3H t)

1 40 ppm (8H, m) 1 8 ppm (3H, m) 2 0 ppm (2H, m) 3 3 ppm (1H, m) 4 4 ppm (2H, q), 8 85 ppm (1H, m)

Step 5

According to M4, 1 02 g (3 81 mmol) of compound A7 (see scheme 1) and 0 5 ml (3 81 mmol) of diethyl sulphate are introduced into a round-bottomed flask and the mixture is then refluxed, with stirring and under nitrogen, for 1 h 30 min After cooling to room temperature, 6 g of ice and 15 ml of HCl (1 2N) are added and this mixture is stirred and then extracted with dichloromethane (3 times 40 ml) The organic phase is dried and concentrated to give 1 1 g of a colourless oil The product is purified by flash chromatography (5/5 CH_2Cl_2/heptane) to give 0 53 g (53%) of a white powder (compound A5, see scheme 1)

Rf (9/1 cyclohexane/ethyl acetate) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

1 4 ppm (11H, m), 1 8 ppm (3H, m) 1 95 ppm (2H, m) 3 1 ppm (1H, m) 4 25 ppm (2H, q) 4 5 ppm (2H, q)

Step 6

5 07 g (17 16 mmol) of compound A5 (see scheme 1) are dissolved in 20 ml of methanol followed by addition of a solution of 1 03 g (25 75 mmol) of sodium hydroxide in 20 ml of water This mixture is stirred at RT for 2 h After evaporating off the methanol, the residue is taken up in CH_2Cl_2 and an identical volume of water is added, followed by addition of concentrated (36%) hydrochloric acid to acidic pH, with stirring The organic phase is dried over Na_2SO_4 and concentrated to give 4 6 g (100%) of a white powder (compound A, see scheme 1)

^1H NMR ($CDCl_3$, 400 MHz),

1 1 ppm to 1 5 ppm (8H m) 3 0 ppm (1H, m) 4 5 ppm (2H, q) 8 4 ppm (1H, m)

Step 7

According to M9, 0 48 g (1 8 mmol) of 5-cyclohexyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 31 g (1 8 mmol) of 2-aminoacetophenone hydrochloride to give a crude amide of type C (see scheme 1)

MS (ES+), m/z = 384 9

Step 8

According to M12, 0 69 g (1 8 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 46 g (5 eq) of tin chloride dihydrate to give 0 103 g (17%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 337

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, m) 7 4 ppm (3H, m) 7 1 ppm (1H, m) 4 5 ppm (2H, q), 4 1 ppm (2H, d) 3 0 ppm (1H, m), 2 0 ppm (2H, m) 1 8 ppm (2H, m) 1 7 ppm (2H, m) 1 5 ppm to 1 2 ppm (7H, m)

EXAMPLE 73

3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-*1H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one

(R1 = cyclohexyl R2 = ethyl R3 = 4-pyridyl)

Synthesis of the pyrazole see steps 1, 2, 3, 5 and 6 of example 72

Step 7

According to M9, 0 48 g (1 8 mmol) of 5-cyclohexylethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid is reacted with 0 376 g (1 8 mmol) of 2-amino-1-pyrid-4-ylethanone hydrochloride (*J Med Chem* , **38**, 17, 3342-3350, 1995, *J Amer Chem Soc* , **67**, 1468-1472, 1945) to give a crude amide of type C (see scheme 1)

MS (ES+), m/z = 385 9

Step 8

According to M12, 0 63 g (1 63 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 12 g (5 eq) of tin chloride dihydrate to give 0 092 g (15%) of the expected product D (see Scheme 1)

m p 126-127°C

MS (ES+) m/z = 338

^{1}H NMR ($CDCl_3$, 400 MHz),

8 6 ppm (2H, d), 7 7 ppm (2H, d) 7 4 ppm (1H, t), 4 5 ppm (2H, q) 4 0 ppm (2H, d), 2 9 ppm (1H, m), 1 9 ppm (2H, m) 1 8 ppm (2H, m) 1 6 ppm (2H, m) 1 4 ppm (3H, m) 1 3 ppm (4H, m)

EXAMPLE 74

3-Cyclohexyl-5-phenyl-1-propyl-6,7-dihydro-*1H*-pyrazolo-[4,3-e][1 4]diazepin-8-one

(R1 = cyclohexyl R2 = propyl R3 = phenyl)

Synthesis of the pyrazole see steps 1, 2 and 3 of example 72 and the following steps 5 and 6

Step 5

According to M5, 2 07 g (28 06 mmol) of Li_2CO_3 are added, under a stream of nitrogen, to a solution of 3 g (11 22 mmol) of compound A7 (see scheme 1) in 60 ml of anhydrous DMF, followed by addition of 2 73 ml (28 06 mmol) of iodopropane The reaction medium is heated at 60°C for 48 h After cooling to room temperature, the mixture is poured into 100 ml of HCl (1 2N) and the exothermicity is controlled by an ice bath This mixture is extracted with dichloromethane (3 times 100 ml) and the organic phase obtained is washed with saturated NaCl solution (100 ml), dried over Na_2SO_4 and concentrated to give 3 6 g of an oily compound This product is purified by flash (gradient 70/30 to 30/70 heptane/CH_2Cl_2) to give 2 85 g (82%) of a

colourless oil which crystallizes (compound A5, see scheme 1)

Rf (60/40 heptane/CH_2Cl_2) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

0 9 ppm (3H, t) 1 45 ppm (6H, m) 1 5 ppm (2H m) 2 85 ppm (7H, m) 3 1 ppm (1H, q) 4 2 ppm (2H, q) 4 4 ppm (2H, q)

Step 6

2 85 g (9 21 mmol) of compound A5 (see scheme 1) are dissolved in 10 ml of methanol, followed by addition of a solution of 0 55 g (13 81 mmol) of sodium hydroxide in 10 ml of water The mixture is stirred at RT for 2 h After evaporating off the methanol, the residue is taken up in CH_2Cl_2 and an identical volume of water is added, followed by addition of concentrated (36%) hydrochloric acid to acidic pH, with stirring The organic phase is dried over Na_2SO_4 and concentrated to give 2 52 g (97%) of a white powder (compound A, see scheme 1)

^1H NMR ($CDCl_3$ 400 MHz),

0 9 ppm (3H, m), 1 2 ppm to 1 6 ppm (5H m) 1 7 ppm to 2 0 ppm (7H, m) 3 1 ppm (1H, m) 4 4 ppm (2H, q), 8 7 ppm (1H, m)

Step 7

According to M9, 0 5 g (1 8 mmol) of 5-cyclohexyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid is reacted with 0 31 g (1 8 mmol) of 2-aminoacetophenone hydrochloride to give a crude amide of type C (see Scheme 1)

MS (ES+), m/z = 399

Step 8

According to M12, 0 72 g (1 8 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 59 g (5 eq) of tin chloride dihydrate to give 0 172 g (27%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 351

^{1}H NMR ($CDCl_3$, 400 MHz),

7 8 ppm (2H, m) 7 4 ppm (4H, m) 4 5 ppm (2H, q) 4 0 ppm (2H, d) 2 9 ppm (1H, m) 1 9 ppm to 1 7 ppm (10H, m) 1 3 ppm (2H, m) 0 9 ppm (3H, t)

EXAMPLE 75

3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-*1H*-pyrazolo-[4,3-e][1,4]diazepin-8-one

(R1 = cyclohexyl R2 = propyl R3 = 4-pyridyl)

Synthesis of the pyrazole see steps 1, 2, 3, 5 and 6 of example 74

Step 7

According to M9, 0 5 g (1 8 mmol) of 5-cyclohexyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid is reacted with 0 376 g (1 8 mmol) of 2-amino-1-pyrid-4-ylethanone hydrochloride (*J Med Chem*, **38**, 17, 3342-3350, 1995 *J Amer Chem Soc*, **67**, 1468-1472, 1945) to give a crude amide of type C (see Scheme 1)

MS (ES+), m/z = 400

Step 8

According to M12, 0 65 g (1 63 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 24 g (5 eq) of tin chloride dihydrate to give 0 055 g (8 6%) of the expected product D (see Scheme 1)

m p 152-153°C

MS (ES+), m/z = 352

^{1}H NMR ($CDCl_3$, 400 MHz),

8 7 ppm (2H, d) 7 7 ppm (2H d) 6 9 ppm (1H, t) 4 4 ppm (2H, m), 4 5 ppm (2H, d) 2 9 ppm (1H, m) 1 9 ppm to 1 6 ppm (10H, m) 1 3 ppm (2H, m) 0 8 ppm (3H, t)

EXAMPLE 76

3-Cyclohexylmethyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = cyclohexylmethyl R2 = ethyl R3 = 4-pyridyl)

Synthesis of the pyrazole see the following steps 1, 2, 5, 3 and 6

Step 1

4 33 g (188 26 mmol) of sodium are dissolved portionwise in 200 ml of anhydrous ethanol under nitrogen at room temperature 25 6 ml (188 26 mmol) of diethyl oxalate in 50 ml of anhydrous ethanol are added 24 g (171 11 mmol) of acetonylcyclohexane are added The reaction mixture is refluxed for 3 h under nitrogen and with stirring, and is then evaporated to dryness and the residue is taken up in 300 ml of HCl (1 2 N) and then extracted with diethyl ether (3 times 200 ml) The organic phase is dried over sodium sulphate and then concentrated to give 42 6 g (92%) of a colourless oil (compound A1, see scheme 1)

Rf (99/1 CH_2Cl_2/acetone) = 0 5

^1H NMR ($CDCl_3$, 400 MHz),

1 0 ppm (2H, m) 1 25 ppm (3H, m) 1 4 ppm (3H, m) 1 7 ppm (6H, m) 1 8 ppm (1H, m) 2 35 ppm (2H, d), 4 4 ppm (2H, q), 6 3 ppm (1H, s) 14 6 ppm (1H, m)

Step 2

12 9 g (195 4 mmol) of potassium hydroxide are dissolved in 250 ml of water and the reaction medium is cooled to 0°C 42 6 g (177 mmol) of compound A1 (see scheme 1) are added portionwise and the mixture is stirred for 30 min at 0°C 25 37 g (195 mmol) of hydrazine sulphate are added and the mixture is then stirred for 45 min at 0°C The resulting mixture is stirred overnight at room temperature, 200 ml of water are then added and this mixture is extracted with dichloromethane (3 times 200 ml) The organic phase

obtained is washed with saturated NaCl solution (1 x 200 ml) and then dried over sodium sulphate and concentrated 40 g of an powder are obtained

The product is purified by flash chromatography (99/1 to 95/5 CH_2Cl_2/acetone) to give 20 7 g (50%) of a white powder (compound A6, see scheme 1)

Rf (97/3 CH_2Cl_2/acetone) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

0 9 ppm (2H, m) 1 2 ppm (4H, m), 1 4 ppm (3H, m), 1 65 ppm (6H, m) 2 6 ppm (H, d) 6 6 ppm (1H, s) 10 5 ppm (1H, m)

Step 5

According to M4, 8 5 g (36 mmol) of compound A6 (see scheme 1) and 2 38 ml (18 mmol) of diethyl sulphate are introduced into a round-bottomed flask and the mixture is then heated at 125-130°C, with stirring and under nitrogen, for 4 h After cooling to room temperature, 120 g of ice and 120 ml of HCl (1 2N) are added with stirring and the resulting mixture is then extracted with dichloromethane (3 times 250 ml) The organic phase is dried and concentrated to give 10 81 g of a brown oil This product is purified by flash chromatography (9/1 cyclohexane/ethyl acetate) to give 5 76 g (60%) of a white powder (compound A8, see scheme 1)

Rf (80/20 cyclohexane/ethyl acetate) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

0 9 ppm (2H, m) 1 2 ppm (4H, m) 1 4 ppm (5H, m) 1 60 ppm (6H, m) 2 5 ppm (2H, d) 4 35 ppm (2H, q) 4 5 ppm (2H, q), 6 6 ppm (1H, s)

Step 3

According to M3, 20 7 g (89 95 mmol) of copper(II) nitrate hemipentahydrate (2 5 H_2O) and 100 ml of trifluoroacetic anhydride are introduced into a round-bottomed flask and the mixture is stirred under nitrogen for 5 min, followed

by addition of 17 g of compound A8 (80 87 mmol) dissolved in 100 ml of chloroform This mixture is refluxed, with stirring and under nitrogen, for 5 hours This product is purified by flash chromatography (98/2 CH_2Cl_2/acetone) to give 20 g of a blueish oil This product is taken up in 200 ml of HCl (1 2N) and then extracted with ether (3 times 300 ml) and the organic phase is dried and concentrated to give 16 81 g (70%) of a colourless oil (compound A5, see scheme 1)

MS (ES+), m/z = 309 90

Rf (70/30 heptane/CH_2Cl_2)= 0 3

^{1}H NMR ($CDCl_3$, 400 MHz),

1 0 ppm (2H, m) 1 2 ppm (3H, m) 1 4 ppm (3H, m), 1 45 ppm (3H, m) 1 7 ppm (6H, m) 2 8 ppm (2H, d) 4 3 ppm (2H, q) 4 5 ppm (2H, q)

Step 6

8 3 g (33 80 mmol) of compound A5 (see scheme 1) are dissolved in 40 ml of methanol, followed by addition of a solution of 2 g (50 7 mmol) of sodium hydroxide in 40 ml of water This mixture is stirred at RT for 2 h After evaporating off the methanol, the residue is taken up in CH_2Cl_2 and an identical volume of water is added, followed by addition of concentrated (36%) HCl to acidic pH, with stirring The organic phase is dried over Na_2SO_4 and concentrated to give 7 5 g (98%) of a white powder (compound A, see scheme 1)

^{1}H NMR ($CDCl_3$, 400 MHz),

1 0 ppm (2H, m) 1 2 ppm (3H, m) 1 5 ppm (3H, t) 1 7 ppm (6H, m) 2 8 ppm (2H, d) 4 6 ppm (2H, q) 8 55 ppm (1H, m)

Step 7

According to M9, 0 281 g (1 8 mmol) of 5-cyclohexylmethyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is

reacted with 0 376 g (1 8 mmol) of 2-amino-1-pyrid-4-ylethanone hydrochloride (*J Med Chem*, **38**, 17, 3342-3350, 1995, *J Amer Chem Soc*, **67**, 1468-1472, 1945) to give a crude amide of type C (see Scheme 1)

MS (ES+), m/z = 400 01

Step 8

According to M12, 0 61 g (1 53 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 02 g (5 eq) of tin chloride dihydrate to give 0 073 g (12%) of the expected product D (see scheme 1)

MS (ES+), m/z = 352 32

^{1}H NMR ($CDCl_3$, 400 MHz),

8 7 ppm (2H, d) 7 8 ppm (2H, d) 7 3 ppm (1H, t) 4 6 ppm (2H, q) 4 1 ppm (2H, d) 2 7 ppm (2H, d) 1 7 ppm (6H, m) 1 5 ppm (3H, t) 1 3 ppm to 1 0 ppm (5H, m)

EXAMPLE 77

3-Cyclohexylmethyl-5-phenyl-1-propyl-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = cyclohexylmethyl, R2 = propyl, R3 = phenyl)

Synthesis of the pyrazole see steps 1 and 2 of example 76 and the following steps 5, 3 and 6

Step 5

According to M5, 3 9 g (52 89 mmol) of Li_2CO_3 are added, under a stream of nitrogen, to a solution of 5 g (21 16 mmol) of compound A6 (see scheme 1) in 100 ml of anhydrous DMF, followed by addition of 5 2 ml (52 89 mmol) of iodopropane The reaction medium is heated at 70°C for 48 h After cooling to room temperature, the mixture is poured into 100 ml of HCl (1 2N) and the exothermicity is controlled with an ice bath This mixture is extracted with dichloromethane (3 times 200 ml) and the organic phase obtained is washed with saturated NaCl solution (200 ml),

dried over Na_2SO_4 and evaporated to dryness to give 5 8 g of a brown oil This product is purified by flash chromatography (gradient 50/50 to 30/70 heptane/CH_2Cl_2) to give 1 15 g (20%) of a colourless oil which crystallizes (compound A8, see scheme 1)

Rf (60/40 heptane/CH_2Cl_2) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

0 9 ppm (5H, m) 1 2 ppm (3H, m) 1 4 ppm (3H, m) 1 7 ppm (6H, m) 1 8 ppm (2H, m) 2 5 ppm (2H, d), 4 3 ppm (2H, q), 4 5 ppm (2H, q) 6 6 ppm (1H, s)

Step 3

According to M3, 0 96 g (4 13 mmol) of copper(II) nitrate hemipentahydrate (2 5 H_2O) and 20 ml of trifluoroacetic anhydride are introduced into a round-bottomed flask and the mixture is stirred under nitrogen for 5 min, followed by addition of 1 15 g of compound A8 (see scheme 1) (4 13 mmol) dissolved in 20 ml of chloroform This mixture is refluxed, with stirring and under nitrogen, for 3 hours This product is taken up in 10 g of ice and 40 ml of HCl (10%) and then extracted with dichloromethane (3 times 100 ml) and the organic phase is dried and concentrated to give 1 3 g of a colourless oil The product is purified by flash chromatography (gradient 70/30 to 50/50 heptane/CH_2Cl_2) to give 1 08 g (80%) of a white powder (compound A5, see scheme 1)

Rf (60/40 heptane/CH_2Cl_2) = 0 3

^1H NMR ($CDCl_3$, 400 MHz),

0 9 ppm (3H, m) 1 0 ppm to 1 3 ppm (5H, m), 1 4 ppm (3H, m) 1 7 ppm (6H, m), 1 9 ppm (2H, m) 2 7 ppm (2H, d), 4 1 ppm (2H, t), 4 5 ppm (2H, q)

Step 6

1 g (3 09 mmol) of compound A5 (see scheme 1) is dissolved in 5 ml of methanol, followed by addition of a solution of 0 185 g (4 64 mmol) of sodium hydroxide in 5 ml of water This mixture is stirred at RT for 2 h After evaporating off the methanol, the residue is taken up in CH_2Cl_2 and an identical volume of water is added, followed by addition of concentrated (36%) hydrochloric acid to acidic pH, with stirring The organic phase is dried over Na_2SO_4 and concentrated to dryness to give 0 89 g (97%) of a white powder (compound A, see scheme 1)

^1H NMR ($CDCl_3$, 400 MHz),

0 9 ppm to 1 0 ppm (5H, m) 1 2 ppm (3H, m), 1 4 ppm (3H, m), 1 6 ppm (6H, m) 1 9 ppm (2H, m) 2 7 ppm (2H, d) 4 1 ppm (2H, t) 4 5 ppm (2H, q)

Step 7

According to M9, 0 463 g (1 57 mmol) of 5-cyclohexylmethyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 269 g (1 57 mmol) of 2-aminoacetophenone hydrochloride to give a crude amide of type C (see scheme 1)

MS (ES+), m/z = 413 04

Step 8

According to M12, 0 65 g (1 57 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 24 g (5 eq) of tin chloride dihydrate to give 0 092 g (14%) of the expected product D (see scheme 1)

MS (ES+), m/z = 364 90

^1H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, m) 7 5 ppm (3H, m) 6 4 ppm (1H, s) 4 5 ppm (2H, m) 4 1 ppm (2H, d) 2 7 ppm (2H, d) 1 9 ppm (2H, m) 1 7 ppm (6H, m) 1 3 ppm to 0 8 ppm (8H, m)

EXAMPLE 78

3-Cyclohexylmethyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = cyclohexylmethyl R2 = propyl R3 = 4-pyridyl)

Synthesis of the pyrazole see steps 1, 2, 5, 3 and 6 of example 77

Step 7

According to M9, 0 464 g (1 57 mmol) of 5-cyclohexylmethyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 328 g (1 57 mmol) of 2-amino-1-pyrid-4-ylethanone hydrochloride (*J Med Chem*, 38, 17, 3342-3350, 1995 *J Amer Chem Soc*, 67, 1468-1472, 1945) to give a crude amide of type C (see Scheme 1)

MS (ES+), m/z = 414 02

Step 8

According to M12, 0 59 g (1 43 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 2 92 g (5 eq) of tin chloride dihydrate to give 0 101 g (15 4%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 366 38

^{1}H NMR ($CDCl_3$, 400 MHz)

8 7 ppm (2H, d) 7 7 ppm (2H, d) 6 9 ppm (1H, m) 4 5 ppm (2H, m) 4 0 ppm (2H, d) 2 7 ppm (2H, d) 1 8 ppm (3H, m) 1 7 ppm (5H, m) 1 0 ppm to 0 8 ppm (8H m)

EXAMPLE 79

3-Cyclohexylmethyl-1-ethyl-5-phenyl-6,7-dihydro-*1H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = cyclohexylmethyl R2 = ethyl R3 = phenyl)

Synthesis of the pyrazole see steps 1 2, 5, 3 and 6 of example 76

Step 5

According to M4, 8 5 g (36 mmol) of compound A6 (see scheme 1) and 2 38 ml (18 mmol) of diethyl sulphate are introduced into a round-bottomed flask and the mixture is then heated at 125-130°C, with stirring and under nitrogen, for 4 h After cooling to room temperature, 120 g of ice and 120 ml of HCl (1 2N) are added and the resulting mixture is stirred and then extracted with dichloromethane (3 times 250 ml) The organic phase is dried and concentrated to give 10 81 g of a brown oil This product is purified by flash chromatography (9/1 cyclohexane/ethyl acetate) to give 5 76 g (60%) of a white powder (compound A8, see scheme 1)

Rf (80/20 cyclohexane/ethyl acetate) = 0 3

^{1}H NMR ($CDCl_3$, 400 MHz),

0 9 ppm (2H, m) 1 2 ppm (4H, m) 1 4 ppm (5H, m), 1 6 ppm (6H, m), 2 5 ppm (2H, d) 4 35 ppm (2H, q), 4 5 ppm (2H, q) 6 6 ppm (1H, s)

Step 3

According to M3, 20 7 g (89 95 mmol) of copper(II) nitrate hemipentahydrate (2 5 H_2O) and 100 ml of trifluoroacetic anhydride are introduced into a round-bottomed flask, this mixture is stirred under nitrogen for 5 min and 17 g of compound A8 (see scheme 1) (80 87 mmol) dissolved in 100 ml of chloroform are then added This mixture is refluxed, with stirring and under nitrogen, for 5 hours This product is purified by flash chromatography (98/2 CH_2Cl_2/acetone) to give 20 g of a blueish oil This product is taken up in 200 ml of HCl (10%) and then extracted with ether (3 times 300 ml) and the organic phase is dried and concentrated to give 16 81 g (70%) of a colourless oil (compound A5, see scheme 1)

MS (ES+), m/z = 309 90

Rf (70/30 heptane/CH_2Cl_2) = 0 3

^{1}H NMR ($CDCl_3$, 400 MHz),

1 0 ppm (2H, m) 1 2 ppm (3H, m) 1 4 ppm (3H, m), 1 45 ppm (3H, m) 1 7 ppm (6H, m) 2 8 ppm (2H d) 4 3 ppm (2H q) 4 5 ppm (2H, q)

Step 6

8 3 g (33 80 mmol) of compound A5 (see scheme 1) are dissolved in 40 ml of methanol, followed by addition of a solution of 2 g (50 7 mmol) of sodium hydroxide in 40 ml of water. This mixture is stirred at RT for 2 h After evaporating off the methanol, the residue is taken up in CH_2Cl_2 and an identical volume of water is added, followed by addition of concentrated (36%) of hydrochloric acid to acidic pH, with stirring The organic phase is dried over Na_2SO_4 and concentrated to dryness to give 7 5 g (98%) of a white powder (compound A see scheme 1)

^{1}H NMR ($CDCl_3$, 400 MHz),

1 0 ppm (2H, m) 1 2 ppm (3H, m) 1 5 ppm (3H, t) 1 7 ppm (6H, m) 2 8 ppm (2H, d) 4 6 ppm (2H q) 8 55 ppm (1H, m)

Step 7

According to M9, 0 281 g (1 8 mmol) of 5-cyclohexylmethyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 309 g (1 8 mmol) of 2-aminoacetophenone hydrochloride to give a crude amide of type C (see scheme 1)

MS (ES+), m/z = 399 60

Step 8

According to M12, 0 72 g (1 8 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 3 59 g (5 eq) of tin chloride dihydrate to give 0 132 g (21%) of the expected product D (see scheme 1)

MS (ES+), m/z = 350 9

^{1}H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (2H, m) 7 4 ppm (3H, m) 7 1 ppm (1H, m) 4 5 ppm (2H, t) 4 0 ppm (2H, d) 2 6 ppm (2H, d) 1 9 ppm (3H, m) 1 6 ppm (5H, m) 1 4 ppm (3H m) 1 1 ppm (3H, m) 0 9 ppm (2H, m)

EXAMPLE 80

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-ylidenecyanamide

(R1 = isopropyl R2 = ethyl R3 = *tert*-butyl)

Step 10

According to M13, 0 96 g (3 28 mmol) of 5-*tert*-butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]-diazepin-8-thione is reacted with 0 0984 g of 80% sodium hydride in refluxing THF for 1 h, followed by addition, at room temperature, of 0 245 ml of methyl iodide The mixture is refluxed for 2 h to give 1 14 g of the expected methylsulphanyl G (see scheme 1)

Rf (95/5 CH_2Cl_2/acetone) = 0 85

MS (ES+), m/z = 307

Step 11

1 g (3 26 mmol) of the methylsulphanyl G (see scheme 1) is reacted with 0 27 g (2 eq) of cyanamide to give 0 825 g (84%) of the expected product of type F (see Scheme 1)

Rf (95/5 CH_2Cl_2/methanol) = 0 56

m p = 243°C

MS (ES+), m/z = 301

^1H NMR ($CDCl_3$, 400 MHz),

8 6 ppm (1H, bs) 4 5 ppm (2H, q) 3 7 ppm (2H, bs) 3 2 ppm (1H, m) 1 4 ppm (3H, t), 1 3 ppm (6H, d) 1 25 ppm (9H, s)

EXAMPLE 81

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo-[4,3-e][1,4]diazepin-8-ylidenecyanamide

(R1 = isopropyl R2 = ethyl R3 = *p*-tolyl)

Step 10

According to M13, 0 61 g (1 87 mmol) of 1-ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]-diazepin-8-thione is reacted with 0 056 g of 80% sodium hydride in refluxing THF for 1 h, followed by addition, at room temperature, of 0 14 ml of methyl iodide The mixture is refluxed for 2 h to give 0 71 g of the expected methylsulphanyl G (see scheme 1)

Rf (95/5 CH_2Cl_2/acetone) = 0 78

MS (ES+), m/z = 341

Step 11

0 64 g (1 87 mmol) of the methylsulphanyl G (see scheme 1) is reacted with 0 16 g (2 eq) of cyanamide to give 0 43 g (69%) of the expected product of type F (see Scheme 1)

Rf (95/5 CH_2Cl_2/methanol) = 0 48

m p = 245°C

MS (ES+), m/z = 335

^1H NMR ($CDCl_3$, 400 MHz),

8 8 ppm (1H, bs), 8 0 ppm (2H, d) 7 3 ppm (2H, d) 4 6 ppm (2H, q) 4 15 ppm (2H, bs) 3 3 ppm (1H, m) 2 4 ppm (3H, s) 1 5 ppm (3H, t) 1 4 ppm (6H d)

EXAMPLE 82

1-Ethyl-3-isopropyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = isopropyl R2 = ethyl R3 = 4-methoxyphenyl)

Step 7

According to M10, 3 18 g (14 mmol) of 2-ethyl-5-isopropyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) are reacted with

2 82 g (14 mmol) of 2-amino-1-(4-methoxyphenyl)ethanone hydrochloride to give 4 7 g (90%) of an amide of type C (see Scheme 1)

MS (ES+), m/z = 375

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, d) 7 7 ppm (1H, t) 7 0 ppm (2H, d) 4 95 ppm (2H, d) 4 25 ppm (2H, q) 3 9 ppm (3H, s) 3 55 ppm (1H, m) 1 5 ppm (3H, t) 1 3 ppm (6H, d)

Step 8

According to M12, 4 7 g (12 5 mmol) of the amide C (see scheme 1) are refluxed in ethanol with 14 2 g of tin chloride dihydrate to give 2 84 g (70%) of the expected product D (see Scheme 1)

MS (ES+), m/z = 327

Rf (95/5 CH_2Cl_2/MeOH) = 0 22

m p = 150°C

^{1}H NMR (DMSO, 400 MHz)

8 25 ppm (1H, t) 8 0 ppm (2H, d) 7 05 ppm (2H, d) 4 45 ppm (2H, q) 4 ppm (2H, d) 3 85 ppm (3H, s) 3 2 ppm (1H, m) 1 35 ppm (3H, t), 1 3 ppm (6H, d)

EXAMPLE 83

Step 9

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione

(R1 = methyl, R2 = ethyl R3 = 4-methoxyphenyl)

2 2 g (7 4 mmol) of 1-ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one are refluxed in toluene with 6 g (14 8 mmol) of Lawesson's reagent to give 2 g (87%) of an expected compound of type E (see Scheme 1)

Rf (95/5 CH_2Cl_2/methanol) = 0 7

m p 209°C

MS (ES+), m/z = 315

^{1}H NMR ($CDCl_3$, 400 MHz),

8 35 ppm (1H bs) 7 95 ppm (2H, d) 6 95 ppm (2H, d) 4 8 ppm (2H, q) 4 15 ppm (2H, bs) 3 9 ppm (3H, s) 2 4 ppm (3H, s) 1 5 ppm (3H, t)

EXAMPLE 84

1-Ethyl-3-methyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-ylidenecyanamide

(R1 = methyl R2 = ethyl R3 = 4-methoxyphenyl)

Step 10

According to M13, 1 75 g (5 6 mmol) of 1-ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione are reacted with 0 23 g of 60% sodium hydride in refluxing THF for 1 h, followed by addition, at room temperature, of 0 42 ml of methyl iodide The mixture is refluxed for 2 h to give 2 g (100%) of the expected methylsulphanyl G (see Scheme 1)

Rf (95/5 CH_2Cl_2/methanol) = 0 86

MS (ES+), m/z = 329

Step 11

2g (6 1 mmol) of the methylsulphanyl G (see Scheme 1) are reacted with 0 52 g (2 eq) of cyanamide to give 1 33 g (68%) of the expected product of type F (see scheme 1)

Rf (95/5 CH_2Cl_2/methanol) = 0 5

m p = 265°C

MS (ES+), m/z = 323

^{1}H NMR (DMSO, 400 MHz),

9 45 ppm (1H, bs), 8 1 ppm (2H, d) 7 1 ppm (2H, d) 4 45 ppm (2H, q) 4 15 ppm (2H, bs) 3 85 ppm (3H, s), 2 3 ppm (3H, s) 1 35 ppm (3H, t)

EXAMPLE 85

3-Isopropyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one
(R1 = isopropyl R2 = propyl R3 = 4-methoxy-phenyle)

Step 7

According to M10, 3 38 g (14 mmol) of 5-isopropyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) are reacted with 2 82 g (14 mmol) of 2-amino-1-(4-methoxyphenyl)ethanone hydrochloride to give 4 58 g (84%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 389

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, d) 7 7 ppm (1H, t), 7 0 ppm (2H, d) 4 95 ppm (2H, d) 4 2 ppm (2H, q) 3 9 ppm (3H, s), 3 55 ppm (1H, m) 1 9 ppm (2H, m) 1 3 ppm (6H, d), 0 95 ppm (3H, t)

Step 8

According to M12, 4 58 g (16 mmol) of the amide C (see scheme 1) are refluxed in ethanol with 13 3 g of tin chloride dihydrate to give 2 92 g (73%) of the expected product D (see scheme 1)

MS (ES+), m/z = 341

^{1}H NMR (DMSO, 400 MHz),

8 2 ppm (1H, t) 8 0 ppm (2H, d) 7 05 ppm (2H, d) 4 4 ppm (2H, q) 4 0 ppm (2H, d) 3 85 ppm (3H, s), 3 2 ppm (1H, m) 1 8 ppm (2H, m) 1 3 ppm (6H, d) 0 85 ppm (3H, t)

Rf (90/10 CH_2Cl_2/acetone) = 0 37

m p = 142°C

EXAMPLE 86

3-*tert*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one
(R1 = *tert*-butyl R2 = ethyl R3 = 4-methoxyphenyl)

Step 7

According to M10, 3 38 g (14 mmol) of 5-*tert*-butyl-2-ethyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) are reacted with 2 82 g (14 mmol) of 2-amino-1-(4-methoxyphenyl)ethanone hydrochloride to give 4 92 g (90%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 389

^{1}H NMR ($CDCl_3$ 400 MHz),

8 0 ppm (2H, d) 7 4 ppm (1H, bs) 7 0 pm (2H d) 4 9 ppm (2H, d) 4 2 ppm (2H, q) 3 9 ppm (3H, s) 1 5 ppm (3H, t) 1 4 ppm (9H, s)

Step 8

According to M12, 4 92 g (13 mmol) of the amide C (see scheme 1) are refluxed in ethanol with 14 3 g of tin chloride hydrate to give 2 1 g (49%) of the expected product D (see scheme 1)

MS (ES+), m/z = 341

Rf (90/10 CH_2Cl_2/acetone) = 0 32

m p = 180°C

^{1}H NMR (DMSO, 400 MHz),

8 3 ppm (1H, t) 8 0 ppm (2H, d) 7 1 ppm (2H, d) 4 4 ppm (2H q) 4 0 ppm (2H d) 3 85 ppm (3H, s) 1 45 ppm (9H, s), 1 35 ppm (3H, t)

EXAMPLE 87

3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

(R1=*tert*-butyl R2=propyl R3=4-methoxyphenyl)

Step 7

According to M10, 3 57 g (14 mmol) of 5-*tert*-butyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) are reacted with 2 82 g (14 mmol) of 2-amino-1-(4-methoxyphenyl)ethanone hydrochloride to give 5 g (89%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 403

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, d) 7 4 ppm (1H t) 6 95 ppm (2H, d) 4 9 ppm (2H, d) 4 1 ppm (2H, q) 3 9 ppm (3H, s) 1 9 ppm (2H, m) 1 4 ppm (9H, s) 0 9 ppm (3H, t)

Step 8

According to M12, 5 g (12 mmol) of the amide C (see scheme 1) are refluxed in ethanol with 14 g of tin chloride dihydrate to give 2 77 g (63%) of the expected product D (see scheme 1)

MS (ES+), m/z = 355

Rf (90/10 CH_2Cl_2/acetone) = 0 37

m p =167°C

^{1}H NMR (DMSO, 400 MHz),

8 3 ppm (1H, t) 8 0 ppm (2H, d) 7 1 ppm (2H, d) 4 4 ppm (2H, q) 4 0 ppm (2H, d) 3 85 ppm (3H, s) 1 8 ppm (2H, m) 1 4 ppm (9H, s) 0 85 ppm (3H, t)

EXAMPLE 88

1-Ethyl-3-methyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-ylidenecyanamide

(R1 = methyl R2 = ethyl R3 = 4-hydroxyphenyl)

0 4 g (1 24 mmol) of 1-ethyl-3-methyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-ylidene-cyanamide is refluxed in dichloromethane with 31 ml of a molar solution of BBr_3 in dichloromethane to give 0 14 g (37%) of the expected product

MS (ES+) m/z = 309

m p = 300 C

Rf (90/10 CH_2Cl_2/MeOH) = 0 55

^{1}H NMR(DMSO, 400 MHz),

10 15 ppm (1H, s) 9 45 ppm (1H, bs) 8 0 ppm (2H, d) 6 9 ppm (2H, d) 4 45 ppm (2H, q) 4 1 ppm (2H, bs) 3 ppm (3H, s) 1 35 ppm (3H t)

EXAMPLE 89

(±)3-*sec*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1=*sec*-butyl R2=ethyl R3=4-methoxyphenyl)

Step 7

According to M10, 3 38 g (14 mmol) of 2-ethyl-5-*sec*-butyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) are reacted with 2 82 g (14 mmol) of 2-amino-1-(4-methoxyphenyl)ethanone hydrochloride to give 4 69 g (86%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 389

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, d) 7 7 ppm (1H, t) 7 0 ppm (2H d) 4 95 ppm (2H, d) 4 3 ppm (2H, q) 3 9 ppm (3H, s) 3 4 ppm (1H, m) 1 85 ppm (1H m) 1 65 ppm (1H, m) 1 5 ppm (3H, t) 1 3 ppm (3H, d) 0 9 ppm (3H, t)

Step 8

According to M12, 4 69 g (12 mmol) of the amide C (see scheme 1) are refluxed in ethanol with 13 6 g of tin chloride dihydrate to give 2 85 g (69%) of the expected product D (see scheme 1)

MS (ES+), m/z = 341

^{1}H NMR (DMSO, 400 MHz),

8 25 ppm (1H, t) 8 ppm (2H, d) 7 05 ppm (2H, d) 4 45 ppm (2H, q) 4 ppm (2H, d) 3 8 ppm (3H, s) 3 ppm (1H, m) 1 75 ppm (1H m) 1 65 ppm (1H, m) 1 35 ppm (3H, t) 1 25 ppm (3H, d) 0 8 ppm (3H, t)

Rf (90/10 CH_2Cl_2/acetone) = 0 29

m p = 50°C

EXAMPLE 90

(±)3-*sec*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = *sec*-butyl R2 = propyl R3 = 4-methoxy-phenyle)

Step 7

According to M10, 3 57 g (14 mmol) of 5-*sec*-butyl-4-nitro-2-propyl-2*H*-pyrazole-3-carboxylic acid (A) are reacted with 2 82 g (14 mmol) of 2-amino-1-(4-methoxyphenyl)ethanone hydrochloride to give 4 77 g (85%) of an amide of type C (see scheme 1)

MS (ES+), m/z = 403

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (2H, d) 7 7 ppm (1H, t) 7 0 ppm (2H, d), 4 95 ppm (2H, d) 4 2 ppm (2H, q) 3 9 ppm (3H s) 3 4 ppm (1H, m) 1 9 ppm (3H, m) 1 6 ppm (1H, m) 1 3 ppm (3H, d) 0 9 ppm (6H, m)

Step 8

According to M12, 4 77 g (12 mmol) of the amide C (see scheme 1) are refluxed in ethanol with 13 4 g of tin chloride dihydrate to give 2 37 g (56%) of the expected product D (see scheme 1)

Rf (90/10 CH_2Cl_2/acetone) = 0 37

m p =85°C

MS (ES+), m/z = 355

^{1}H NMR (DMSO 400 MHz),

8 25 ppm (1H, t) 8 0 ppm (2H, d) 7 05 ppm (2H, d) 4 4 ppm (2H, q) 4 0 ppm (2H, m), 3 8 ppm (3H, s) 3 0 ppm (1H, m) 1 75 ppm (3H, m) 1 65 ppm (1H m) 1 25 ppm (3H, d) 0 8 ppm (6H, m)

EXAMPLE 91

1-Ethyl-3-methyl-5-(3,4,5-trimethoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
(R1 = methyl R2 = ethyl R3 = 3,4,5-trimethoxyphenyl)

Step 7

According to M10, 0 153 g (0 77 mmol) of 2-ethyl-5-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid (A) is reacted with 0 246 g (0 77 mmol) of 2-amino-1-(3,4,5-trimethoxyphenyl)-ethanone hydrochloride (78%) (*J Org Chem*, 38, 3571-3575, 1973) to give 0 313 g (83%) of an amide of type C (see scheme 1)

Rf (CH_2Cl_2/MeOH 95/5) = 0 78

^{1}H NMR ($CDCl_3$, 400 MHz),

8 0 ppm (1H, bs) 7 2 ppm (2H, d) 5 0 ppm (2H, d), 4 3 ppm (2H, q) 3 9 ppm (9H s) 2 6 ppm (3H, s) 1 5 ppm (3H, t)

Step 8

According to M12, 0 26 g (0 64 mmol) of the amide C (see scheme 1) is refluxed in ethanol with 0 72 g of tin chloride dihydrate to give 0 13 g (57%) of the expected product D (see scheme 1)

Rf (95/5 CH_2Cl_2/MeOH) = 0 52

m p = 208°C

MS (ES+), m/z = 359

^{1}H NMR (DMSO, 400 MHz),

8 25 ppm (1H, t) 7 3 ppm (2H, s) 4 45 ppm (2H, q) 4 0 ppm (2H, d) 3 9 ppm (6H, s) 3 7 ppm (3H, s), 2 3 ppm (3H, s) 1 35 ppm (3H, t)

EXAMPLE 92

1-Ethyl-5-(3-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo [4 3-e][1,4]diazepin-8-one
(R1 = methyl R2 = ethyl R3 = 3-hydroxyphenyl)

0 4 g (1 34 mmol) of 1-ethyl-5-(3-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is

441

refluxed in dichloromethane with 33 5 ml of a molar solution of BBr_3 in dichloromethane to give 0 075 g (20%) of the expected product

MS (ES+) m/z = 285

m p = 204 C

Rf (90/10 CH_2Cl_2/MeOH) = 0 55

^1H NMR (DMSO, 400 MHz),

9 65 ppm (1H s) 8 25 ppm (1H, m) 7 45 ppm (2H, m) 7 3 ppm (1H, m) 6 9 ppm (1H, m) 4 4 ppm (2H, q) 3 95 ppm (2H, d) 2 3 ppm (3H, s) 1 35 ppm (3H, t)

EXAMPLE 93

1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = methyl R2 = ethyl R3 = 2-hydroxyphenyl)

0 4 g (1 34 mmol) of 1-ethyl-5-(2-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is refluxed in dichloromethane with 33 5 ml of a molar solution of BBr_3 in dichloromethane to give 0 070 g (19%) of the expected product

MS (ES+) m/z = 285

m p = 220 C

Rf (90/10 CH_2Cl_2/MeOH) = 0 7

^1H NMR (DMSO, 400 MHz),

14 0 ppm (1H, s) 8 35 ppm (1H, m) 7 8 ppm (1H, m) 7 4 ppm (1H, m) 7 0 ppm (2H, m) 4 45 ppm (2H, q) 4 2 ppm (2H, d) 2 3 ppm (3H, s) 1 35 ppm (3H, t)

EXAMPLE 94

1-Ethyl-5-(4-hydroxyphenyl)-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

(R1 = isopropyl R2 = ethyl R3 = 4-hydroxyphenyl)

0 5 g (1 53 mmol) of 1-ethyl-5-(4-methoxy-phenyl)-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is refluxed in dichloromethane with 38 ml of a molar solution of BBr_3 in dichloromethane to give 0 23 g (48%) of the expected product

MS (ES+) m/z = 313

m p = 230°C

Rf (90/10 CH_2Cl_2/MeOH) = 0 27

^1H NMR (DMSO 400 MHz),

10 0 ppm (1H, s) 8 2 ppm (1H, t) 7 85 ppm (2H, d) 6 85 ppm (2H d) 4 4 ppm (2H q) 3 9 ppm (2H d) 3 2 ppm (1H, m) 1 35 ppm (3H, t) 1 3 ppm (6H, d)

EXAMPLE 95

5-(4-Hydroxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4)diazepin-8-one

(R1 = isopropyl R2 = propyl R3 = 4-hydroxyphenyl)

0 5 g (1 47 mmol) of 5-(4-methoxyphenyl)-3-isopropyl-1-propyl-5-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one is refluxed in dichloromethane with 37 ml of a molar solution of BBr_3 in dichloromethane to give 0 2 g (42%) of the expected product

MS (ES+) m/z = 327

m p = 230°C

Rf (90/10 CH_2Cl_2/MeOH) = 0 38

^1H NMR (DMSO, 400 MHz),

10 0 ppm (1H s) 8 2 ppm (1H, t) 7 85 ppm (2H, d) 6 85 ppm (2H, d) 4 4 ppm (2H q) 3 9 ppm (2H, d) 3 2 ppm (1H, m) 1 8 ppm (2H m) 1 3 ppm (6H, d) 0 85 ppm (3H, t)

EXAMPLE 96

3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6 7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one

(R1 = *tert*-butyl R2 = ethyl R3 = 4-hydroxyphenyl)

0 5 g (1 47 mmol) of 1-*tert*-butyl-5-(4-methoxyphenyl)-3-isopropyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one is refluxed in dichloromethane with 1 4 ml of BBr_3 to give 0 29 g (60%) of the expected product

MS (ES+) m/z = 327

m p = 264°C

Rf (90/10 CH_2Cl_2/MeOH) = 0 4

^1H NMR (DMSO, 400 MHz),

10 0 ppm (1H, s) 8 2 ppm (1H, t) 7 85 ppm (2H, d) 6 85 ppm (2H, d) 4 4 ppm (2H q) 3 9 ppm (2H d) 1 4 ppm (9H, s) 1 3 ppm (3H, t)

EXAMPLE 97

3-Ethoxymethyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one

(R1 = ethoxymethyl R2 = ethyl R3 = phenyl)

Step 19

8 1 g (22 mmol) of compound R (see scheme 3) are reacted with 49 ml of ethylene glycol and 0 81 g (4 3 mmol) of para-toluenesulphonic acid monohydrate in 170 ml of toluene After 48 hours about 40 ml of water have been removed (Dean-Stark apparatus) The reaction mixture is treated with saturated $NaHCO_3$ solution and water and the phases are then allowed to separate by settling The organic phase is dried over Na_2SO_4 and concentrated The oil obtained is chromatographed on silica with an 80/20 cyclohexane/EtOAc mixture to give 6 6 g (73%) of the expected compound S (see scheme 3)

Rf (70/30 cyclohexane/EtOAc) = 0 28

MS (ES+), m/z = 418 9

^{1}H NMR ($CDCl_3$, 400 MHz),

7 3-7 55 ppm (6H, m) 4 4-4 5 ppm (4H m) 4 1 ppm (2H, q) 3 8 ppm (4H, m) 1 5 ppm (3H, t) 1 4 ppm (3H, t)

Step 20

1 5 g (3 6 mmol) of compound S (see scheme 3) are reacted with 4 3 ml (8 6 mmol) of a 2M solution of lithium borohydride in THF, in 25 ml of anhydrous THF After 12 hours at room temperature, the reaction mixture is extracted with water and diethyl ether The organic phase is dried over Na_2SO_4 and concentrated to give 1 2 g (96%) of the expected compound T (see scheme 3)

Rf (95/5 CH_2Cl_2/MeOH) = 0 17

MS (ES+), m/z = 347

^{1}H NMR (DMSO, 400 MHz),

8 65 ppm (1H, m) 7 3-7 5 ppm (5H, m) 4 9 ppm (1H t) 4 4 ppm (2H, d) 4 3 ppm (2H q) 4 05 ppm (2H, t) 4 0 ppm (2H, s) 3 8 ppm (2H, t) 3 7 ppm (2H d) 1 2 ppm (3H, t)

Step 21

0 3 g (0 9 mmol) of compound T (see scheme 3) is reacted with 15 ml of ethanol and 15 ml of 6N HCl at 80 C After 12 hours, the reaction mixture is concentrated and the residue obtained is extracted with water and dichloromethane The organic phase is dried over Na_2SO_4 and concentrated and then chromatographed on silica using an elution gradient of from 100% dichloromethane to a 95/5 dichloromethane/MeOH mixture to give 0 023 g (8 5%) of the compound D (see scheme 3) (RB = ethyl)

Rf (95/5 CH_2Cl_2/MeOH) = 0 27

MS (ES+), m/z = 313

^{1}H NMR ($CDCl_3$, 400 MHz),

7 9 ppm (2H, m) 7 45 ppm (3H, m) 6 0 ppm (1H, m) 4 75 ppm (2H s) 4 6 ppm (2H, q) 4 15 ppm (2H, d) 3 65 ppm (2H, q) 1 5 ppm (3H, t) 1 25 ppm (3H, t)

448

445

EVALUATION OF THE BIOLOGICAL ACTIVITY OF THE COMPOUNDS OF THE PRESENT INVENTION

Evaluation of the *in vitro* activity of the compounds of the examples

The capacity of the compounds of formula (I) of the invention to inhibit cyclic nucleotide phosphodiesterases is evaluated by measuring their IC_{50} (concentration needed to inhibit 50% of the enzymatic activity) In the case of PDE4 enzymes, this value is compared to the IC_{50} value for rolipram, a reference inhibitor for PDE4 enzymes

The type 4 phosphodiesterases are obtained from a cytosolic preparation extracted from a cell line of human origin, U937 according to the method adapted from T J Torphy et al 1992, J Pharm Exp Ther 263 1195-1205

The other types of phosphodiesterase are obtained during a partial purification by FPLC on a Mono Q column (anion exchange column) according to a method adapted from Lavan B E , Lakey T , Houslay M D Biochemical Pharmacology, 1989 38(22) 4123-4136 and Silver P J et al , 1988 Eur J Pharmacol 150 85-94, either starting with cell lines of human origin for PDE1 (monocyte line TPH1) and PDE5 (line derived from an adenocarcinoma MCF7), or starting with dog aorta for PDE3 or, for human PDE3A, starting with a cloning of genes in SF21 insect cells into baculovirus, according to the method adapted from Luckow, V A et al , 1991 in Recombinant DNA Technology & Applications , eds Prokop, Bajpai, R K & Ho, C S , pp 97-152

Table 1

Example	IC_{50} (μM)	Example	IC_{50} (μM)	Example	IC_{50} (μM)	Example	IC_{50} (μM)
1	0 0049	25	0 0024	50	0 016	75	0 0049
2	0 00098	26	0 0056	51	0 06	76	0 0082
3	0 00012	27	0 0038	52	0 00065	77	0 21
4	0 0084	28	0 090	53	0 26	78	0 021
5	0 39	29	0 33	54	0 24	79	0 011
6	0 42	30	0 30	55	0 0017	80	0 00022
7	0 13	31	0 19	56	0 50	81	0 00054
8	0 21	32	0 13	57	0 00013	82	0 062
9	0 15	33	0 11	58	0 14	83	0 10
10	1 29	34	0 0047	59	0 51	84	0 060
11	0 12	35	0 00070	60	0 58	85	0 20
12	0 10	36	0 00039	61	0 0079	86	0 31
13	0 13	37	0 00097	62	0 26	87	0 041
14	0 081	38	0 65	63	0 0050	88	0 0021
15	0 52	39	0 0091	64	0 0046	89	0 033
16	0 42	40	0 0082	65	0 0015	90	0 193
17	0 0059	41	0 011	66	0 00063	91	0 90
18	0 10	42	0 010	67	0 0010	92	0 092
19	0 087	43	0 048	68	0 0062	93	0 0074
20	0 099	44	0 0011	69	0 013	94	0 0021
21	0 0026	45	0 0026	70	0 011	95	0 015
22	0 028	46	0 00084	71	0 035	96	0 0049
23	0 042	47	0 021	72	0 0018	97	1 58
24	0 078	48	0 0081	73	0 00073		
		49	0 032	74	0 0054	Rolipram	0 859

Examination of the results of Table 1 shows that the products of the invention tested in the study generally inhibit the PDE4 enzyme of human origin much more

effectively than rolipram, and in certain cases these products are between 3 000 and 4 000 times more active than rolipram

Evaluation of the *in vivo* activity of the compounds of the invention

***in vivo* TNFα Model in Wistar rats**

TNFα is a cytokine which plays a central role in the mechanisms of inflammation Its production can be induced by an injection of lipopolysaccharide (LPS) It has been shown that the increase in intracellular cAMP, produced in particular by PDE4 inhibitors, decreases the production of TNFα in *in vitro* and *in vivo* models It is thus a matter here of quantifying *in vivo* the anti-inflammatory potential of the compounds of the invention administered orally (p o) by measuring the inhibition of the production of TNFα in the plasma of rats, these rats having received an intraperitoneal (i p) injection of lipopolysaccharide (LPS) The treatment with the compounds of the invention or the vehicle are [sic] administered orally to male Wistar rats, 30 min before the injection of LPS The rats are sacrificed 90 min after the stimulation with LPS, the blood is collected onto EDTA and the TNFα concentration is measured in each plasma sample Most of the compounds of the invention and in particular the compounds hereinbelow showed excellent activity in this model

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

5-(4-Aminophenyl)-1-ethyl-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-(2-Hydroxyethyl)-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one
1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1 4]diazepin-8-one,
1-Ethyl-3-methyl-5-p-tolyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one,
5-(3-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-tert-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1H-pyrazolo[4,3-*e*][1,4]diazepin-8-thione
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-thione
5-(4-Aminophenyl)-3-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-Cyclohexyl-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one,
5-*tert*-Butyl-1-ethyl-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1 4]diazepin-8-one,

4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

5-(2 4-Dimethoxyphenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one

5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1 4]diazepin-8-one,

3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

4-(3-Isopropyl-8-oxo-1-propyl-1,6,7,8-tetrahydro-pyrazolo-[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

4-(3-*tert*-Butyl-1-ethyl-8-oxo-1 6 7 8-tetrahydropyrazolo-[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

1-Ethyl-3-methyl-5-phenyl-1,6-dihydropyrazolo-[4,3-*e*][1 4]diazepin-8-ylcyanamide,

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1 4]diazepin-8-ylidenecyanamide,

(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one,

(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo-[4,3-*e*][1,4]diazepin-8-one

<u>References</u>

Chen, Y L , Le Vraux, V Giroud, J P and Chauvelot-Moachon L (1994) Anti-tumor necrosis factor properties of

non-peptide drugs in acute-phase responses Eur J Pharmacol 271 (2-3) 319-27

Prabhakar, U , Lipshutz, D O'Leary Barthus, J , Slivjak, J , Smith III E F , Lee, J C and Esser K M (1994) Characterization of cAMP-dependent inhibition of LPS-induced TNFa production by rolipram a specific phosphodiesterase IV (PDE IV) inhibitor Int J Immunopharmacol , 16 (10), 805-816

Model of eosinophilia in rats

The studies carried out using this experimental model have the aim of evaluating the inhibitory activity of the compounds of the invention on the afflux of inflammatory cells and in particular of eosinophils in the lumen of the bronchotracheal tree of rats Eosinophils play a major role in the physiopathology of asthma in man by releasing into the pulmonary parenchyma pro-inflammatory mediators such as leukotrienes, specific proteins and enzymes (ECP, EPO, MBP) and cytokines The massive recruitment of this cell type in the aerial pathways of an asthmatic leads to a gradual degradation of the pulmonary tissue, which explains the bronchial hyperreactivity, the chronic aspect of the disease and the exacerbations in the absence of treatment This model uses Brown Norway rats, which have the particular feature of producing, like atopic patients, high levels of immunoglobulin E (IgE) in response to a sensitization by an antigen The protocol used involves two sensitizations with ovalbumin with a fourteen-day interval, followed by a challenge seven days later with an ovalbumin aerosol 48 hours after the antigenic challenge, the animals undergo bronchoalveolar lavage under anaesthesia in order to collect the infiltrate of inflammatory cells on

the lungs These cells are then counted and differentiated according to morphological criteria The products of the invention are administered orally 1 hour before the antigenic challenge Most of the compounds of the present invention tested in this model also demonstrated excellent activity

References

Corrigan et al (1992) Immunology today 13 501-507
Elwood et al (1995) Inflamm Res 44 83-86

Model of neutrophilia in mice

The studies carried out using this experimental protocol have the aim of evaluating the modulatory action of the compounds of the invention on the afflux of pro-inflammatory cells (early phase) in the lumen of the bronchotracheal tree of mice This cellular afflux follows a stimulation mimicking a bacterial infection (bacterial lipopolysaccharide or LPS) This early inflammatory stage is the result of a combination of events, the main ones of which are the synthesis and release of stimulatory factors ($TNF\alpha^{i}$) and chemotactic factors ($IL\text{-}8^{ii}$), the increase in vascular permeability in the bronchotracheal microcirculation, and the infiltration of polymorphonuclear neutrophils^{iii} concomitant with the exudation of plasma proteins into the pulmonary tissues

This pathological process is found in chronic obstructive bronchopneumopathy (or COPD), in which the neutrophil, in concert with the macrophage, plays a key role in establishing the amplification of the recruitment of the

neutrophils themselves, but also in the destructuring of pulmonary tissues (decline in pulmonary functions), the hypersecretion of bronchotracheal mucus (congestion of the aerial pathways), tissue inflammation (release of inflammatory mediators and free radicals) and increase in the basal tonus of pulmonary smooth muscle fibres (chronic respiratory gene) Most of the compounds of the present invention tested in this model demonstrated excellent activity

References

[i] SUTER P M , SUTER S , GIRARDIN E , ROUX-LOMBARD P , GRAU G E and DAYER J -M 1992 High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon and elastase, in patients with adult respiratory distress syndrome after trauma, shock or sepsis *Am Rev Respir Dis* 145 1016-1022

[ii] MARTIN T R and GOODMAN R B 1999 The role of chemokines in the pathology of the acute respiratory distress syndrome Chapter 6 in Chemokines in disease Biology and clinical research edited by C A Hébert, Humana Press Inc , Totowa, NJ

[iii] REPINE J E and BEEHLER C J 1991 Neutrophils and the adult respiratory distress syndrome two interlocking perspectives *Am Rev Respir Dis* 144 251-252

Jejunal inflammation and septic shock induced by E coli lipopolysaccharide in rats

Lipopolysaccharide (LPS) from Escherichia coli administered intravenously to fasted male Wistar rats induces an inflammation of the jejunum two hours later

Male Wistar rats (200-280 g) fasted (18 h), from the Sté Janvier Le-genest-St Isle, Mayenne, France are used in these experiments

The compounds to be tested are suspended in a vehicle (1% methylcellulose (95% v/v) + polyethylene glycol 400 (5% v/v)) They are then administered orally (5 ml/kg) using a stainless steel probe, one hour before administration of the inducing agent (LPS) The groups of animals are distributed in the following manner

- Negative controls p o vehicle + serum i v physiological saline
- Positive controls p o vehicle + LPS
- Treated p o compound + LPS

The lipopolysaccharide (LPS), endotoxin from Escherichia coli (serotype 0127 B8) is then injected intravenously (caudal vein) at a dose of 40 mg/kg (5 ml/kg) to conscious rats maintained under slight support

Two hours later, the animals are sacrificed, the abdomen is opened and a 10 cm section of jejunum (30th to 40th after the pylorus) is taken, cut in the direction of its length, mopped and weighed

The macroscopic attack is evaluated (0 = none, 1 = slight, 2 = moderate, 3 = severe)

After weighing, the segment is fixed onto a flat surface and measurements of the percentage of hyperhemiated surfaces are made using an image analyser

Immediately after analysis, the tissue is deposited in 10 ml of Drabkin reagent to determine the haemoglobin content of the tissue (colorimetric assay 24 hours later) Most of the compounds of the present invention tested in this model demonstrated excellent activity

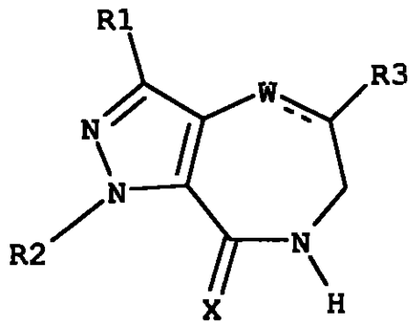
Lipopolysaccharide (LPS) Sigma, reference L-3880, France
Polyethylene glycol M W 400 Sigma, reference P-3265
Haemoglobin content of the jejunum Sigma kit, Total heamoglobin, reference 525-A

Main reference

Cardelus Ignasi *et al* European Journal of Pharmacology 299 (1996) 153-159

CLAIMS

1 Compound of formula I below



I

in which

R1 is chosen from the following groups

hydrogen

linear or branched alkyl containing from 1 to 6 carbon atoms

cycloalkyl containing from 3 to 6 carbon atoms

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

arylalkyl containing from 6 to 10 carbon atoms optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

linear or branched alkenyl containing from 2 to 6 carbon atoms

the groups $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nC(S)R_B$, $(CH_2)_nC(S)OR_B$, $(CH_2)_nC(S)SR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, $(CH_2)_nNR_DC(O)NR_DR_B$ or $(CH_2)_nZ$, in which,

R_A is chosen from linear or branched alkyl containing from 1 to 6 carbon atoms

cycloalkyl containing from 3 to 6 carbon atoms

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

linear or branched alkenyl containing from 2 to 6 carbon atoms

R_B and R_C, which may be identical or different, are chosen from hydrogen

linear or branched alkyl containing from 1 to 6 carbon atoms

cycloalkyl containing from 3 to 6 carbon atoms

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen oxygen and sulphur,

linear or branched alkenyl containing from 2 to 6 carbon atoms

it being possible for R_B and R_C to form a ring containing from 5 to 7 atoms which can include one or more hetero atoms chosen from S, N and O

R_D is hydrogen or linear or branched alkyl containing from 1 to 6 carbon atoms

Z is a halogen and

n is an integer from 0 to 4 inclusive

R2 is chosen from the following groups

linear or branched alkyl containing from 1 to 6 carbon atoms

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

cycloalkyl containing from 3 to 6 carbon atoms

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

linear or branched alkenyl containing from 2 to 6 carbon atoms

the groups $(CH_2)_mOR_B$, $(CH_2)_nCF_3$, $(CH_2)_mC(O)R_B$, $(CH_2)_mCOOR_B$, $(CH_2)_mOC(O)R_A$ $(CH_2)_mSR_B$, $(CH_2)_mC(S)R_B$, $(CH_2)_mC(S)OR_B$, $(CH_2)_mC(S)SR_B$ $(CH_2)_mNR_BR_C$, $(CH_2)_mC(O)NR_BR_C$, $(CH_2)_mNR_CC(O)R_B$, $(CH_2)_mNR_DC(O)NR_DR_B$ or $(CH_2)_mZ$, in which,

R_A, R_B, R_C R_D and Z are as defined above, and

m is an integer from 1 to 4 inclusive

n is an integer from 0 to 4 inclusive

R3 is chosen from the following groups

hydrogen

linear or branched alkyl containing from 1 to 6 carbon atoms

cycloalkyl containing from 3 to 6 carbon atoms

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms,

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

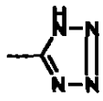
linear or branched alkenyl containing from 2 to 6 carbon atoms

the groups $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nC(S)R_B$, $(CH_2)_nC(S)OR_B$, $(CH_2)_nC(S)SR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$, $(CH_2)_nNR_DC(O)NR_DR_B$ or $(CH_2)_nZ$, in which,

R_A R_B, R_C R_D and n are as defined above

the aryl, arylalkyl and alkylaryl groups defined above being unsubstituted or substituted on the aryl group with 1 2 or 3 groups chosen from

halogen, hydroxyl, NO, NO_2, CN, alkoxy containing from 1 to 4 carbon atoms, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, $(CH_2)_nHNSO_2R_B$, $(CH_2)_nN(SO_2R_B)_2$, CO_2R_B, CF_3 and



in which R_B, R_C and n are as defined above and

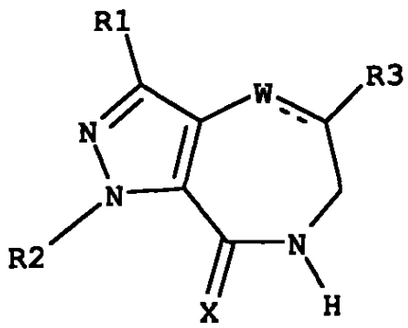
the dotted line present in formula I indicates that the bond between W and the carbon in position 5 may be

- a single bond, in which case W represents a nitrogen atom substituted with a hydrogen atom,
- a double bond, and in this case W represents an unsubstituted nitrogen atom

X is S, O, N-CN or N-R_8 in which R_8 is as defined above

as well as the oxides, the tautomeric forms and the corresponding opticals isomers or the pharmaceutically acceptable derivatives of the compounds of formula I,
with the proviso that when
R1 represents a methyl group, R2 an ethyl group, W is N, X is an oxygen atom and the bond between W and the carbon in position 5 is a double bond,
then
R3 is neither an unsubstituted phenyl group nor a phenyl group bearing a fluorine atom in an ortho position as sole substituent

2 Compounds of the formula I below



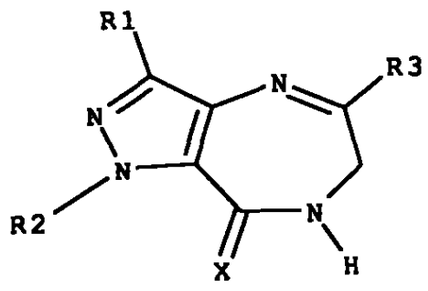
I

in which R1, R2, R3 et X are as defined in Claim 1, W represents an unsubstituted nitrogen atom and the bond

between W and the carbon in position 5, symbolized by ----, is a double bond

as well as the oxides, the tautomeric forms and corresponding isomers or the pharmaceutically acceptable derivatives of the compounds of formula I,
with the proviso that when,
R1 represents a methyl group R2 an ethyl group, W is N, X is an oxygen atom and the bond between W and the carbon in position 5 is a double bond, then
R3 is neither an unsubstituted phenyl group nor a phenyl group bearing, as sole substituent, a fluorine atom in an ortho position

3 Compound according to Claim 1 or 2, of formula II below



II

in which

R1 is a linear or branched alkyl group containing from 1 to 6 carbon atoms
a cycloalkyl group containing from 3 to 6 carbon atoms
an alkylcycloalkyl group comprising an alkyl group containing from 1 to 6 carbon atoms and a

cycloalkyl group containing from 3 to 6 carbon atoms

an aryl group containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen oxygen and sulphur

an arylalkyl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

an alkylaryl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

a linear or branched alkenyl group containing from 2 to 6 carbon atoms

the groups $(CH_2)_nOR_B$, $(CH_2)_nCF_3$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nSR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$ or $(CH_2)_nZ$, in which

R_A is chosen from linear or branched alkyl containing from 1 to 6 carbon atoms

cycloalkyl containing from 3 to 6 carbon atoms

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen oxygen and sulphur

alkylaryl containing from 6 to 10 carbon atoms optionally interrupted with a hetero

atom chosen from nitrogen, oxygen and sulphur

linear or branched alkenyl containing from 2 to 6 carbon atoms

R_B and R_C, which may be identical or different, are chosen from hydrogen

linear or branched alkyl containing from 1 to 6 carbon atoms

cycloalkyl containing from 3 to 6 carbon atoms

alkylcycloalkyl comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

aryl containing from 5 to 10 carbon atoms optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

arylalkyl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen oxygen and sulphur

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

linear or branched alkenyl containing from 2 to 6 carbon atoms

R_B and R_C possibly forming a ring containing from 5 to 7 atoms which may include one or more hetero atoms chosen from S, N or O

Z is a halogen and

n is an integer from 0 to 4 inclusive

R2 is a linear or branched alkyl group containing from 1 to 4 carbon atoms

$(CH_2)_nCF_3$ in which n is an integer from 0 to 4 inclusive

methylcyclopropyl

linear or branched alkenyl containing from 2 to 6 carbon atoms

or a group $(CH_2)_mOR_B$ and $(CH_2)_mCO_2R_B$, in which m is an integer from 1 to 3 inclusive and R_B is as described above

R3 is a linear or branched alkyl group containing from 1 to 6 carbon atoms

a cycloalkyle group containing from 3 to 6 carbon atoms

an alkylcycloalkyl group comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

an aryl group containing from 5 to 10 carbon atoms optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

an arylalkyl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

an alkylaryl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

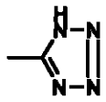
a linear or branched alkenyl group containing from 2 to 6 carbon atoms

the groups $(CH_2)_nOR_B$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$ and $(CH_2)_nNR_CC(O)R_B$, in which,

R_A, R_B, R_C and n are as defined above

the aryl, arylalkyl and alkylaryl groups defined above being unsubstituted or substituted on the aryl group with 1, 2 or 3 groups chosen from

halogen, hydroxyl, NO, NO_2, CN, alkoxy containing from 1 to 4 carbon atoms, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, $(CH_2)_nHNSO_2R_B$ $(CH_2)_nN(SO_2R_B)_2$, CO_2R_B, CF_3 and



in which R_B, R_C and n are as defined above and,

X is O, S or NCN

4 Compound according to Claim 1 or 2, in which

R1 is a linear or branched alkyl group containing from 1 to 6 carbon atoms

a cycloalkyl group containing from 3 to 6 carbon atoms

an alkylcycloalkyl group comprising an alkyl group containing from 1 to 6 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

an aryl group containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

an alkylaryl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

a linear or branched alkenyl group containing from 2 to 6 carbon atoms

the groups $(CH_2)_nOR_B$, $(CH_2)_nC(O)R_B$, $(CH_2)_nCOOR_B$, $(CH_2)_nOC(O)R_A$, $(CH_2)_nNR_BR_C$, $(CH_2)_nC(O)NR_BR_C$, $(CH_2)_nNR_CC(O)R_B$ or $(CH_2)_nZ$, in which,

R_A is chosen from linear or branched alkyl containing from 1 to 6 carbon atoms,

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

R_B and R_C, which may be identical or different, are chosen from hydrogen,

linear or branched alkyl containing from 1 to 6 carbon atoms,

aryl containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

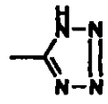
alkylaryl containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur,

n is an integer from 0 to 4 inclusive;

R2 is a linear or branched alkyl group containing from 1 to 4 carbon atoms or a group $(CH_2)_mOH$ or $(CH_2)_mCO_2H$, in which m is an integer from 1 to 3 inclusive,

R3 is a linear or branched alkyl group containing from 1 to 6 carbon atoms
a cycloalkyl group containing from 3 to 6 carbon atoms
an aryl group containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur
an arylalkyl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur
an alkylaryl group containing from 6 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur

the aryl, arylalkyl and alkylaryl groups defined above being unsubstituted or substituted on the aryl group with 1, 2 or 3 groups chosen from
halogen, hydroxyl, NO, NO_2, CN, alkoxy containing from 1 to 4 carbon atoms, $(CH_2)_nOR_B$, $(CH_2)_nNR_BR_C$, $(CH_2)_nNC(O)R_B$, CO_2R_B, CF_3 and



in which R_B, R_C and n are as defined above and

X is O, S or NCN

5 Compound according to Claim 1 or 2, in which

R1 is a linear or branched alkyl group containing from 1 to 4 carbon atoms
a cycloalkyl group containing from 3 to 6 carbon atoms

an alkylcycloalkyl group comprising an alkyl group containing from 1 to 3 carbon atoms and a cycloalkyl group containing from 3 to 6 carbon atoms

R2 is a linear or branched alkyl group containing from 1 to 4 carbon atoms

R3 is a linear or branched alkyl group containing from 1 to 4 carbon atoms
an aryl group containing from 5 to 10 carbon atoms, optionally interrupted with a hetero atom chosen from nitrogen, oxygen and sulphur, preferably phenyl or pyridyl, the aryl groups being unsubstituted or substituted with 1, 2 or 3 groups, which may be identical or different, chosen from NH_2, halogen, methoxy, hydroxyl, CN, CH_3 and CF_3, and,

X is O, S or NCN

6 Compound according to Claim 1 or 2, in which

R1 is a linear or branched alkyl group containing from 1 to 4 carbon atoms

R2 is a linear or branched alkyl group containing from 1 to 4 carbon atoms or a group $(CH_2)_nOH$, in which n is an integer from 1 to 4 inclusive

R3 is a linear or branched alkyl group containing from 1 to 4 carbon atoms, a cycloalkyl group containing from 3 to 6 carbon atoms, an aryl group

chosen from phenyl and thienyl, which may be unsubstituted or substituted with a group chosen from halogen, hydroxyl, methoxy, NH_2 and CH_3 and

X is S or O

7 Compound according to Claims 1 to 6, chosen from the group consisting of
1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1,3-Dimethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Methoxyphenyl)-1,3-dimethyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one,
5-(4-Bromophenyl)-1,3-dimethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
1-Ethyl-3-methyl-5-naphth-2-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(3-Chlorothien-2-yl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
Methyl 3-(1-ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)propanoate,
1-Ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
5-(4-Chlorophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-fluorophenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-(3-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Isopropyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

(±)1-Ethyl-3-methyl-5-phenyl-4 5 6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-(2-Hydroxyethyl)-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

1-Ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-5-(3-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-(2-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

1-Ethyl-5-(2-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-3-methyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one, isomer 1,

1-Ethyl-3-methyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one, isomer 2,

3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

1-Ethyl-3-methyl-5-p-tolyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-(3-Aminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-thione,

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

5-(4-Aminophenyl)-3-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one

1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-(4-Aminophenyl)-3-methyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Methyl-5-phenyl-1-(2,2,2-trifluoroethyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1,5-Diethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-Cyclohexyl-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

1-Ethyl-3-methyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

(±)1-Ethyl-3-methyl-5-pyrid-4-yl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-*tert*-Butyl-1-ethyl-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-(4-Diethylaminophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

N-[4-(1-Ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1 4]diazepin-5-yl)phenyl]acetamide,

4-(1-Ethyl-3-methyl-8-oxo-1 6,7,8-tetrahydropyrazolo[4 3-e][1,4]diazepin-5-yl)benzonitrile,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4,3-e][1,4]diazepin-5-yl)benzonitrile,
1-Ethyl-3-isopropyl-5-(4-pyrrolidin-1-yl-phenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(2,4-Dimethoxyphenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-Isopropyl-1-propyl-5-*p*-tolyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
4-(3-Isopropyl-8-oxo-1-propyl-1,6,7,8-tetrahydropyrazolo[4,3-e][1,4]diazepin-5-yl)benzonitrile,
3-Isopropyl-1-propyl-5-(4-pyrrolidin-1-yl-phenyl)-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-one,
5-(2,4-Dimethoxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
3,5-Di-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
4-(3-*tert*-Butyl-1-ethyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4 3-e][1,4]diazepin-5-yl)benzonitrile,
3-*tert*-Butyl-1-ethyl-5-(4-pyrrolidin-1-yl-phenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

3,5-Di-*tert*-butyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-*tert*-Butyl-8-oxo-1-propyl-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
3-tert-Butyl-1-propyl-5-(4-pyrrolidin-1-yl-phenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,
3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-methyl-5-pyrid-3-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-pyrid-2-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-phenyl-1,6-dihydropyrazolo[4,3-*e*][1,4]diazepin-8-ylcyanamide,
N-[4-(1-Ethyl-3-methyl-8-oxo-1 6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)phenyl]-(phenylsulphonyl)benzenesulphonamide,
(1-Ethyl-3-methyl-5-phenyl-1,6-dihydropyrazolo[4,3-*e*][1,4]diazepin-8-yl)methylamine,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-ylidenecyanamide,
1-Cyclopentyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Cyclopropylmethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,
1-Cyclobutylmethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Allyl-3-methyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-(4-trifluoromethylphenyl)-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione
3,5-Di-*tert*-butyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Lthyl-3-isopropyl-5-*p*-tolyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-5-phenyl-1-propyl-4-yl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one,
(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexyl-1-ethyl-5-phenyl-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexyl-5-phenyl-1-propyl-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexylmethyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexylmethyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexylmethyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
3-Cyclohexylmethyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-8-oxo-5-phenyl-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-3-carboxylic acid ethyl ester,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
1-Ethyl-3-isopropyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
3-Isopropyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3e][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
(±)3-*sec*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

(±)3-*sec*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-(3,4,5-trimethoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-5-(3-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-one,
1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one,
1-Ethyl-3-methyl-5-(2,3,4-trimethoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3,5-diphenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Hydroxyphenyl)-3-isopropyl-1-propyl-6,7-dihydrp-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(2,6-Dimethoxyphenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-Ethoxymethyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one

8 Compound according to Claims 1 to 6, chosen from the group consisting of
1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-naphth-2-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(3-Chlorothien-2-yl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

Methyl 3-(1-ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-e][1,4]diazepin-5-yl)propanoate,
5-(4-Chlorophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(4-Aminophenyl)-1-ethyl-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-5-(4-fluorophenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(3-Bromophenyl)-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one
3-Methyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-(2-Hydroxyethyl)-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione,
1-Ethyl-5-(3-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(2-Aminophenyl)-1-ethyl-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-5-(2-methoxyphenyl)-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-p-tolyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
5-(3-Aminophenyl)-1-ethyl-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-thione,

1-Ethyl-3-isopropyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-(4-Aminophenyl)-3-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one
5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Aminophenyl)-3-methyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Methyl-5-phenyl-1-(2,2,2-trifluoroethyl)-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-Cyclohexyl-1-ethyl-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,
5-*tert*-Butyl-1-ethyl-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
5-(2,4-Dimethoxyphenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

4-(3-Isopropyl-8-oxo-1-propyl-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
5-(2,4-Dimethoxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3,5-Di-*tert*-butyl-1-ethyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-*tert*-Butyl-1-ethyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1 4]diazepin-5-yl)benzonitrile,
3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3,5-Di-*tert*-butyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-*tert*-Butyl-8-oxo-1-propyl-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
3-*tert*-Butyl-5-(2,4-dimethoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-methyl-5-pyrid-3-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-pyrid-2-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-phenyl-1,6-dihydropyrazolo[4,3-*e*][1,4]diazepin-8-ylcyanamide,
N-[4-(1-Ethyl-3-methyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)phenyl]-(phenylsulphonyl)benzenesulphonamide,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,

3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
1-Cyclopropylmethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Allyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
1-Ethyl-3-methyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-(4-trifluoromethylphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
3,5-Di-*tert*-butyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-*tert*-Butyl-3-isqpropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-5-phenyl-1-propyl-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,
3-Cyclohexyl-1-ethyl-5-phenyl-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexyl-5-phenyl-1-propyl-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1 4]diazepin-8-one,

3-Cyclohexylmethyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexylmethyl-5-phenyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexylmethyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexylmethyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-8-oxo-5-phenyl-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-3-carboxylic acid ethyl ester,

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,

1-Ethyl-3-isopropyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,

3-Isopropyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one,

1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
(±)3-*sec*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one
(±)3-*sec*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-(3,4 5-trimethoxyphenyl)-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(3-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3,5-diphenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Hydroxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Ethoxymethyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

9 Compound according to Claims 1 to 6, chosen from the group consisting of
1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-5-(2-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1H-pyrazolo[4,3-e][1,4]diazepin-8-thione,

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-thione,

5-(4-Aminophenyl)-3-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one,

5-Cyclohexyl-1-ethyl-3-methyl-6 7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

1-Ethyl-3-methyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

5-*tert*-Butyl-1-ethyl-3-methyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one,

4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-e][1,4]diazepin-5-yl)benzonitrile,

5-(2,4-Dimethoxyphenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1 4]diazepin-8-one,

5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4 3-e][1,4]diazepin-8-one,

3-Isopropyl-1-propyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-e][1,4]diazepin-8-one

4-(3-Isopropyl-8-oxo-1-propyl-1,6,7,8-tetrahydropyrazolo[4,3-e][1,4]diazepin-5-yl)benzonitrile,

5-(2,4-Dimethoxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
3,5-Di-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-*tert*-Butyl-1-ethyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-methyl-5-phenyl-1,6-dihydropyrazolo[4,3-*e*][1,4]diazepin-8-ylcyanamide,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-one,
3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexylmethyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
1-Ethyl-3-isopropyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-methoxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
3-Isopropyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,
(±)3-*sec*-Butyl-1-ethyl-5-(4-methoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-methyl-5-(3,4,5-trimethoxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(3-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3,5-diphenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Hydroxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Ethoxymethyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

10 Compound according to Claims 1 to 6, chosen from the group consisting of

1-Ethyl-3-methyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1H-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-(4-Aminophenyl)-3-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-Isopropyl-8-oxo-1-propyl-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
3,5-Di-*tert*-butyl-1-ethyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-*tert*-Butyl-1-ethyl-8-oxo-1,6,7,8-tetrahydropyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,

3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

1-Ethyl-3-methyl-5-phenyl-1 6-dihydropyrazolo[4 3-*e*][1,4]diazepin-8-ylcyanamide,

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-ylidenecyanamide

3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1 4]diazepin-8-ylidenecyanamide,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,

(±)3-*sec*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexyl-1-ethyl-5-pyrid-4-yl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-Cyclohexylmethyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-*tert*-Butyl-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,

1-Ethyl-3-isopropyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide,

1-Ethyl-5-(4-hydroxyphenyl)-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

5-(4-Hydroxyphenyl)-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

11 Compound according to Claims 1 to 6, chosen from the group consisting of

1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one
3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-phenyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
5-*tert*-Butyl-3-isopropyl-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
4-(3-Isopropyl-8-oxo-1-propyl-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile,
3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione,
(±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
(±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,

3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one,
1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide

12 1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

13 3-*tert*-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

14 1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione

15 5-(4-Aminophenyl)-1-ethyl-3-isopropyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

16 1-Ethyl-5-(4-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

17 4-(1-Ethyl-3-isopropyl-8-oxo-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1,4]diazepin-5-yl)benzonitrile

18 5-*tert*-Butyl-3-isopropyl-1-propyl-6 7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

19 4-(3-Isopropyl-8-oxo-1-propyl-1,6,7,8-tetrahydro-pyrazolo[4,3-*e*][1 4]diazepin-5-yl)benzonitrile

20 3-*tert*-Butyl-1-ethyl-5-*p*-tolyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

21 3-Butyl-1-ethyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-thione

22 (±)3-*sec*-Butyl-1-ethyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4 3-*e*][1,4]diazepin-8-one

23 (±)3-*sec*-Butyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

24 3-Cyclohexyl-1-propyl-5-pyrid-4-yl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

25 3-*tert*-Butyl-5-(4-methoxyphenyl)-1-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

26 1-Ethyl-5-(2-hydroxyphenyl)-3-methyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

27 3-*tert*-Butyl-1-ethyl-5-(4-hydroxyphenyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-one

28 1-Ethyl-3-isopropyl-5-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*e*][1,4]diazepin-8-ylidenecyanamide

29 Pharmaceutical composition comprising at least one compound defined according to any one of Claims 1 to 28, in combination with a pharmaceutically acceptable support

30 Compound according to any one of Claims 1 to 28, for its use as a medicinal product

31 Compound according to any one of Claims 1 to 28, for its use as a medicinal product for treating complaints

including cancer, acquired immunodeficiency syndrome, fibrosis, excessive scarring including excessive dermal scarring such as normal or abnormal dermal scarring following wounding or surgery, osteoarthritis, osteoporosis, multiple sclerosis, anxiety, depression, atopic dermatitis, rheumatoid arthritis, septic shock, immune diseases including disseminated lupus erythematous, psoriasis, graft rejection and allergic rhinitis, as well as diseases involving the production of TNFα, inflammatory complaints such as asthma chronic obstructive bronchopneumopathy (COPD), post-ischaemic lesions, pulmonary hypertension, congestive cardiac insufficiency, acute respiratory distress syndrome, and chronic inflammatory diseases of the intestine (IBD) such as Crohn's disease and ulcerative colitis

32 Compound according to any one of Claims 1 to 28, for its use as a medicinal product for treating inflammatory complaints comprising chronic obstructive bronchopneumopathy, asthma and chronic inflammatory diseases of the intestine (IBD) such as Crohn's disease and ulcerative colitis

33 Compound according to any one of Claims 1 to 28, for its use as a medicinal product for treating inflammatory complaints comprising chronic obstructive bronchopneumopathy and asthma

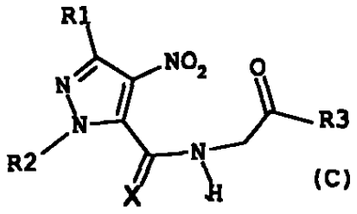
34 Method for treating a disease or complaint involving a treatment with a phosphodiesterase 4 inhibitor, the said method comprising the administration to a patient of an effective concentration of a compound of formula I according to any one of Claims 1 to 28

35 Use of a compound of general formula I according to any one of Claims 1 to 28, to prepare a medicinal product for treating complaints involving a therapy with a phosphodiesterase 4 inhibitor

36 Process for preparing a compound according to any one of Claims 1 to 28, comprising the following steps

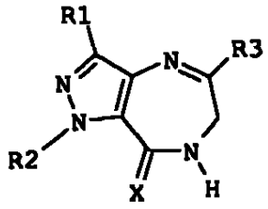
1) when, in formula I, X is O or S, W is N and the bond between W and the carbon in position 5, symbolized by ----, is a double bond

- the cyclization of a compound of general formula (C)



(C)

in which R1, R2, R3 and X have the meaning given above, to give a synthetic intermediate or a final compound of general formula D,



(D)

in which R1, R2, R3 and X have the meanings given above

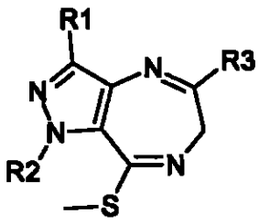
2) when, in formula I, X is S, W is N and the bond between W and the carbon in position 5, symbolized by ----, is a double bond

the thionation of a compound of general formula (D), in which R1, R2 and R3 have the meaning given above

and X is O, to give a compound of formula I in which the bond between W and the carbon atom in position 5 is a double bond, W is N and X is sulphur

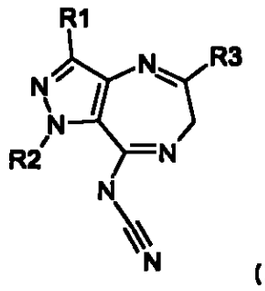
3) when in formula I X is N-CN, W is N and the bond between W and the carbon in position 5, symbolized by ----- , is a double bond

the reaction of a compound of general formula (G)



(G)

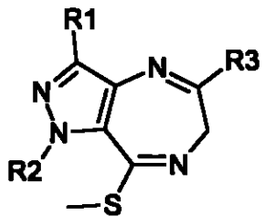
in which R1, R2 and R3 have the meaning given above, with a compound of formula H_2N-CN, to give a compound of general formula F below



(F)

4) when, in formula I, X is N-R_8, W is N and the bond between W and the carbon in position 5, symbolized by ----- , is a double bond

the reaction of a compound of general formula (G)

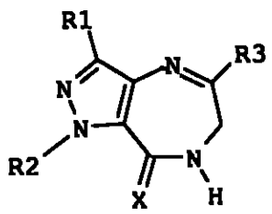


(G)

in which R1, R2 and R3 are as defined above, with a compound of formula H_2N-R_8 in which R_8 is as defined above, to give a compound of formula I in which the bond between W and the carbon atom in position 5 is a double bond, W is N and X is $N-R_8$

5) when, in formula I, W is NH and the bond between W and the carbon in position 5 is a single bond

the reaction of a compound of general formula (D)

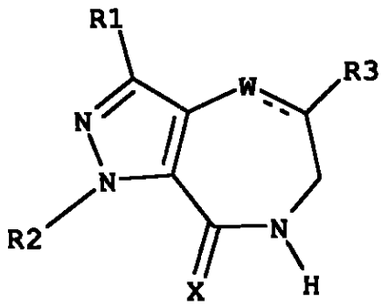


(D)

in which R1, R2, R3 and X are as defined above, with a reducing agent, to give a compound of formula I in which W is NH and the bond between W and the carbon in position 5 is a single bond

ABSTRACT

The invention relates to novel substituted pyrazolo[4,3-e]-diazepines of general formula

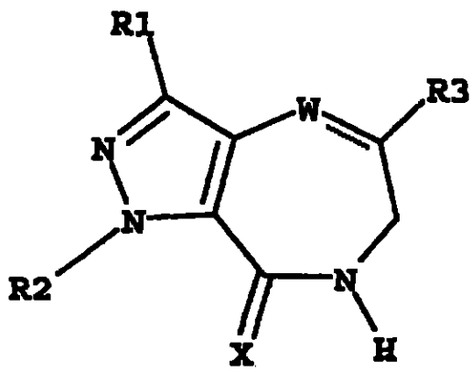


I

to pharmaceutical compositions containing them, to their use as medicinal products and to processes for preparing them

Folio 508 Arte final
30-10-02

Folios 500 y 501 a 507
tal cual


R1
R3
W
N
N
R2
N
X
H

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE

497

PATENTE DE INVENCIÓN [X] **MODELO DE UTILIDAD [ ]**

- Indicacion de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de Pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación grafica y fotografica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicacion de que se solicita el registro de un Esquema de trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema de trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

SUPERINDUSTRIA Y COMERCIO
Fecha Radicacion : 01000514 0000000 Folios 509
Fecha (RAD) 2001-01-04 15:03:25
Tramite 002 PATENTES D 1 REGISTRO 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

Carrera 13 No 27-00 Piso 5 y 10
Conmutador 334 12 21-2-3-4
Fax 281 31 25 e-mail info@sic.gov.co
Santa Fe de Bogotá D C. -Colombia

Industria y Comercio
SUPERINTENDENCIA

INFORME DE PROTOCOLO

Expediente 01-514

Fecha 2 de abril del 2001

498

Se certifica que

Desde fecha 22 de octubre de 1997,

del folio 94.235 al folio 94.238 del libro de Protocolo N° 323 obra el documento N° 17.877 conferido por WARNER-LAMBERT COMPANY domiciliado(a) en Morris Plains, New Jersey. E.U.A.

al doctor DANIEL GOYTIA quien a su vez sustituye a "RODRIGUEZ Y ASOCIADOS" Y/O RODOLFO RODRIGUEZ MADRID Y/O CARLOS JULIO BUITRAGO GARZON Y/O MARINA RODRIUEZ MADRID

OBSERVACIONES: En el libro se encuentra protocolizada la sustitución, pero no el poder concedido al abogado DANIEL GOYTIA por la sociedad arriba mencionada Tampoco consta dentro del mismo la existencia y representanción legal de la sociedad (8 de Agosto del 2000)

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

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá D C

499

Doctor
RODOLFO RODRIGUEZ MADRID

REFERENCIA	Radicación No	01 514
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No	1042
	Folios	001

Como resultado del examen de forma realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina se le comunica que

Para un mejor entendimiento y posterior digitalización de la solicitud es importante que los documentos presentados estén legibles y completos por lo tanto debe aportar un nuevo capítulo descriptivo y reivindicatorio

Con el fin de reconocer personería al abogado que presenta la solicitud debe allegarse el poder concedido al abogado que realiza la sustitución debido a que dentro del protocolo 17877 únicamente reposa la sustitución que del poder hace el doctor Daniel Goytia Adicionalmente debe presentarse el documento que acredita la existencia y representación legal de la sociedad solicitante

Debe indicarse el lugar de constitución de la sociedad solicitante (Art. 27-c D 486/00)

Debe allegar comprobante de pago por exceso de 150 palabras del extracto de publicación

Debe allegar copia del documento en que consta la cesión del derecho a la patente otorgado por el inventor al solicitante o a su causante (art. 26-k,Dec 486/2000)

En cumplimiento del artículo 39 de la Decisión 486 de la Comisión de la Comunidad Andina se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio complete los requisitos anteriormente enunciados En caso de no dar cumplimiento al presente requerimiento la solicitud se considerará abandonada y perderá su prelación

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la Resolución Reglamentaria No 210 del 15 de enero del 2001

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 05 ABR 2001

Se recuerda al interesado que debe presentar dentro de los dieciséis meses siguientes contados a partir de la fecha de presentación de la solicitud cuya prioridad se invoca copia de la misma certificada por la autoridad que la expidió y en los casos en que haya lugar la traducción simple del capítulo reivindicatorio. El incumplimiento de éste plazo, acarreará el abandono de la prioridad invocada

202027/202022

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