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SUPERINDUSTRIA Y COMERCIO
Radicación : 00065062 00000007 Folios: 13
Fecha (AMH): 2006-01-13 17:56:02
Trámite : 002 PATENTES D 1 REGISTRO/ 444 RESPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: Expediente No. 00.065.062

Solicitud de patente titulada: "LOS INHIBIDORES TRICICLICOS DE POLI (ADP-RIBOSA) POLIMERASAS".

Solicitante: AGOURON PHARMACEUTICALS INC, y CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED.

RESPUESTA AL OFICIO No. 9704 NOTIFICADO POR FIJACION EN LISTA No. 418.
DE FECHA 20 DE OCTUBRE 2005, (PRIMER EXAMEN DE FONDO)

J. IAN RAISBECK, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado sustituto, tal como consta en la sustitución adjunta, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486, en los siguientes términos:

1. El Examinador objeta la claridad de la presente invención con base en los siguientes argumentos:

"En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"

Las reivindicaciones 1 a 17, en primer lugar no están soportadas enteramente en la descripción, porque reclaman un "metabolito activo, prodrug" de los compuestos de la fórmula reclamada, y no se describe ningún metabolito activo, ni tampoco algún profármaco (prodrug) de los millones de compuestos reclamados, son términos amplios y especulativos, que en realidad son características deseables para los compuestos, no son compuestos definidos de manera inequívoca como lo indica el artículo en referencia.

Además el termino (sic) "prodrug", es un termino (sic) que no esta (sic) en el idioma castellano, y tal como se indico (sic) antes es un termino (sic) vago y especulativo, que no delimita el alcance de la invención.

En la reivindicación 19 existe un absurdo, porque se cambia el significado universalmente conocido del elemento F (flor), y se dice que "F es hidrógeno".

Las reivindicaciones 8, 9 y 13 pretenden definir los compuestos, por resultados farmacológicos a obtener, o por características o propiedades deseables, con lo cual no define, ni delimita perfectamente el alcance de la invención."

2 a- Con el propósito de acoger los comentarios del Examinador, me permito hacer los siguientes cambios en el Capítulo Reivindicatorio:

- (a) **MODIFICAR** las Reivindicaciones 1 a 7, 10 a 14, 16 y 17, de tal modo que los términos "prodrug" y "metabolito activo" se eliminan de dichas reivindicaciones.
- (b) **DESISTIR** de las Reivindicaciones 8 y 9, las cuales refieren características farmacológicas de los compuestos descritos.
- (c) **MODIFICAR** la Reivindicación 19 de tal modo que se muestra la formula química estructural del compuesto reclamado. El error que menciona el Examinador obedece a un problema de traducción y por tanto se anexa este gráfico para definir perfectamente el compuesto.
- (d) **ADICIONAR** una nueva reivindicación (actual Reivindicación 18), la cual reclama específicamente el compuesto 1-[4-(1-metil-piperidin-4-il)-fenil]-8,9-dihidro-7H-2,7,9a-triaza-benzo[cd]azulen-6-ona. Esta nueva reivindicación no implica ampliación alguna del concepto inventivo, ya que se refiere al compuesto que ilustra el ejemplo 141 del Capítulo Descriptivo la presente invención (página 114).



Con base en lo anterior, el nuevo Capítulo Reivindicatorio es como se muestra a continuación:

Capítulo Reivindicatorio Original	Capítulo Reivindicatorio Modificado
Reivindicación 1.	Reivindicación 1. MODIFICADA*
Reivindicación 2.	Reivindicación 2. MODIFICADA*
Reivindicación 3.	Reivindicación 3. MODIFICADA*
Reivindicación 4.	Reivindicación 4. MODIFICADA*
Reivindicación 5.	Reivindicación 5. MODIFICADA*
Reivindicación 6.	Reivindicación 6. MODIFICADA*
Reivindicación 7.	Reivindicación 7. MODIFICADA*
Reivindicación 8.	ELIMINADA
Reivindicación 9.	ELIMINADA
Reivindicación 10.	Reivindicación 8. MODIFICADA*
Reivindicación 11.	Reivindicación 9. MODIFICADA*
Reivindicación 12.	Reivindicación 10. MODIFICADA*
Reivindicación 13.	Reivindicación 11. MODIFICADA*
Reivindicación 14.	Reivindicación 12. MODIFICADA*
Reivindicación 15.	Reivindicación 13.
Reivindicación 16.	Reivindicación 14. MODIFICADA*
Reivindicación 17.	Reivindicación 15. MODIFICADA*
Reivindicación 18.	Reivindicación 16.
Reivindicación 19.	Reivindicación 17. MODIFICADA* ¹
	Reivindicación 18. ADICIONADA

*: Se eliminaron los términos “prodrug” y “metabolito activo”

*¹: Se agregó la fórmula estructural del compuesto reivindicado.

b- Respecto a la objeción que hace el Examinador a la Reivindicación 13 (ahora Reivindicación 11), quiero respetuosamente manifestar mi desacuerdo, ya que dicha reivindicación reclama una composición farmacéutica compuesta de:

- (a) *una cantidad eficaz de agente inhibidor-PARP, seleccionado a partir de los compuestos definidos en la afirmación 1, o sales farmacéuticas o solvatos de los mismos;*
- (b) *un portador farmacéuticamente aceptado para dicho agente inhibidor-PARP,*



OLARTE RAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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y no define tal composición por los resultados farmacológicos a obtener, o por características o propiedades deseables, como afirma el Examinador. Aunque el encabezado de la Reivindicación describe "*una cantidad eficaz de agente inhibidor-PARP*", perfectamente se aclara que tal agente es un compuesto como los descritos en la Reivindicación 1 (o una sal farmacéuticamente aceptable o un solvato del mismo); claramente, la reivindicación describe composiciones constituidas por un compuesto como los descritos en la Reivindicación 1 y un vehículo farmacéuticamente aceptable.

3. Con base en los argumentos aquí presentados, le solicito respetuosamente al Examinador que evalúe de nuevo los requisitos de patentabilidad y le otorgue el privilegio de patente a la presente invención.

Atentamente,

J. IAN RAISBECK
C.C. 79.376.996 de Bogotá
T.P. 135.799

Anexos: Capítulo Reivindicatorio Modificado
Sustitución de Poder

1952

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO DE CONTENIDO Y FIRMA.

NOTARIA EL ANTERIOR ESCRITO DIGNO A:

27 FUE PRESENTADO PERSONALMENTE ANTE EL SUSCRITO NOTARIO VEINTISIETE DE SANTIAGO DE BOGOTA POR:

[Signature]

En CC. *[Signature]* EL *[Signature]* DEL ANTERIOR DUEÑO DE LA CASA Y QUE LA FIRMA QUE LO AUTENTICA ES LA DEL NOTARIO POR EL.

[Signature] HUY

9 ENE 2006 HUE

MARIA EUGENIA ROJAS DE CHUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

Comercio

6613579902



OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

Servicios Legales y Profesionales

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Nit 830 122 870-6
office@olarteraisbeck.com
www.olarteraisbeck.com

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

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Solicitud de patente titulada: "LOS INHIBIDORES TRICICLICOS DE POLI(ADP-RIBOSA)
POLIMERASAS".

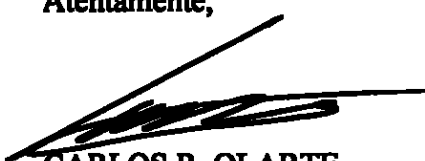
Solicitante: AGOURON PHARMACEUTICALS INC, y CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED.

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que SUSTITUYO el poder a mi conferido por la mencionada sociedad, en el doctor J. IAN RAISBECK LLINAS, mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.376.996 de Bogotá y portador de la Tarjeta Profesional No. 135.799 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,


CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295 del C. S. de la J.

052

DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA.

NOTARIA EL ANTERIOR ESCRITO DIRIGIDO A:
Super. Industria y Comercio

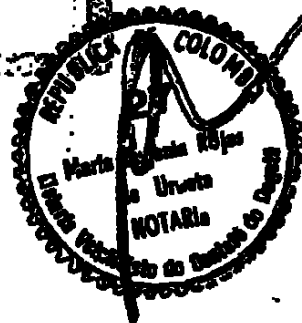
27 FUE PRESENTADO PERSONALMENTE
POR EL SUSCRITO NOTARIO VEINTISIETE
DE SANTAE DE DEGRUA POR:
Carlos R. Olarte

Con C.C. *22.982.772.61* L.P. *74.295.651*

DECLARA NOTARIO QUE EL CONTENIDO DEL ANTERIOR
DOCUMENTO ES VERDADERO Y QUE EL FIRMANTE ES EL
MISMO QUE EL QUE SE ENCUENTRA EN EL
DOCUMENTO.

18 ABR. 2005 HUELLA

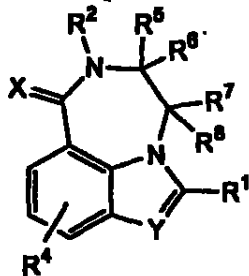
MARIA EZEQUIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA



524
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SE AFIRMA LO SIGUIENTE:

1. Un compuesto de la fórmula:



en donde:

X es O u S;

Y es N o CR³, donde R³ es: ~~—~~ H;

halógeno;

ciano;

un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo; o

-C(W)-R²⁰, donde W es O u S, y R²⁰ es: H; OH; un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, heteroarilo, O-alquilo, o grupo O-arilo; o NR²⁷R²⁸, donde R²⁷ y R²⁸ son cada uno independientemente H, OH, o un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo;

-CR²⁹=N-R³⁰, donde R²⁹ es H o un amino sustituido opcionalmente, alquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo, y R³⁰ es H, OH, un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, heteroarilo, O-alkyl, o grupo O-arilo, o NR³¹R³², donde R³¹ y R³² son cada uno independientemente H, OH, o un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo;

R^1 es

H;

halógeno;

ciano;

un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo;

$C(O)R^{12}$, donde R^{12} es: H; un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo; o OR^{19} o $NR^{21}R^{22}$, donde R^{19} , R^{21} y R^{22} son cada uno independientemente H o un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo;

OR^{13} , donde R^{13} es H o un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo;

$S(O)_nR^{16}$, donde n es 0, 1 o 2, y R^{16} es: H; un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo; o $NR^{23}R^{24}$, donde R^{23} y R^{24} son cada uno independientemente H o un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo; o

$NR^{17}R^{18}$, donde R^{17} y R^{18} son cada uno independientemente: H; un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo; o $S(O)_2NR^{25}N^{26}$, donde R^{25} y R^{26} son cada uno independientemente H o un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo;

R^2 es H o alquilo;

R^4 es H, halógeno, o alquilo;

R^5 , R^6 , R^7 , y R^8 son cada uno independientemente seleccionados a partir de:

H;

un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo; y

$-C(O)-R^{50}$, donde R^{50} es: H; un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo; o OR^{51} o $NR^{52}R^{53}$, donde R^{51} , R^{52} y R^{53} son cada uno independientemente H o un alquilo sustituido opcionalmente, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, o grupo heteroarilo;

en donde cuando Y es CR^3 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , y R^8 no son todos H;

o una sal farmacéuticamente aceptable o un solvato del mismo.

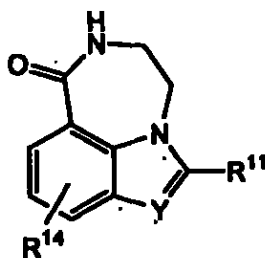
2. Un compuesto de acuerdo con la afirmación 1, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde R^1 es no sustituido, arilo mono- o di-sustituido o heteroarilo.

3. Un compuesto de acuerdo con la afirmación 1, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde R^4 es H o halógeno.

4. Un compuesto de acuerdo con la afirmación 1, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde R^5 , R^6 , R^7 y R^8 son cada uno H.

5. Un compuesto de acuerdo con la afirmación 1, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde X es oxígeno.

6. Un compuesto de fórmula:



en donde:

Y es tal como definido en la afirmación 1;

R^{11} es un grupo arilo o heteroarilo no sustituido o sustituido con uno o más de los sustituyentes seleccionados de halógeno, hidroxilo, nitro, amino, alquilo, arilo, heteroarilo, alkoxy, arilooxy, y grupos heteroarilooxy, en donde dichos alquilo, arilo, heteroarilo, alkoxy, arilooxy, y grupos heteroarilooxy son no

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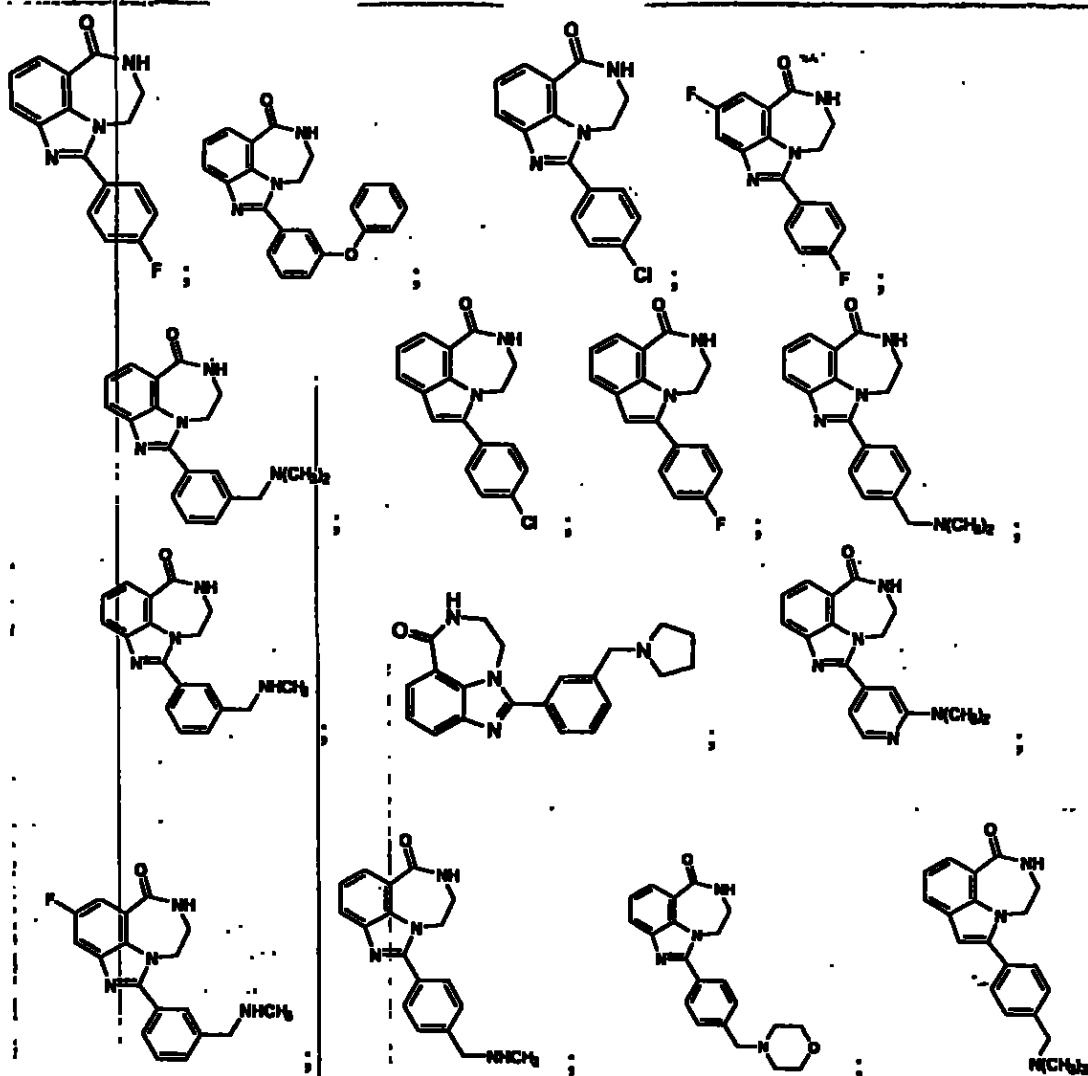
sustituidos o sustituidos con uno o mas de los sustituyentes seleccionados del halógeno, hidroxilo, alcoxilo inferior, ciano, nitro, y amino; y

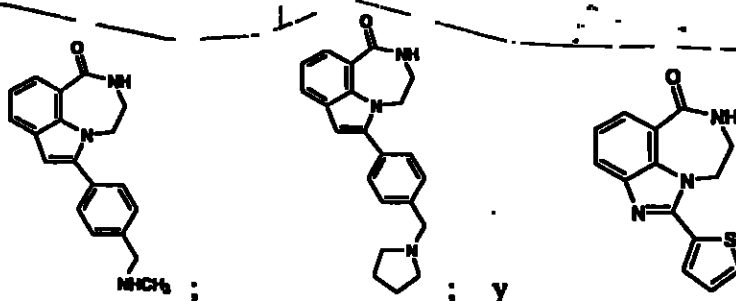
R^{14} es H o halógeno;

o una sal farmacéuticamente aceptable o un solvato del mismo.

7 Un compuesto de acuerdo con la afirmación 6, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde R^{14} es fenilo mono- o di-sustituido.

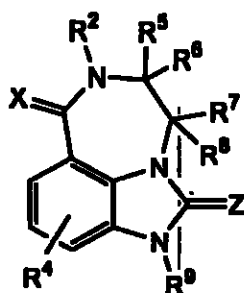
8 Un compuesto de acuerdo a la afirmación 1, seleccionado del grupo que consiste en:





o una sal farmacéuticamente aceptable o un solvato del mismo.

9. Un compuesto de la formula:



en donde:

Z es O o S;

R⁹ es H o alquilo; y

todas las demás variantes son tal como se definen en la afirmación 1;

o una sal farmacéuticamente aceptable o un solvato del mismo.

10. Un compuesto de acuerdo con la afirmación 9, o una sal farmacéuticamente aceptable o un solvato del mismo, en donde R² y R⁹ son cada uno independientemente H o metilo, R⁴ es H o halógeno, R⁵, R⁶, R⁷ y R⁸ son cada uno H, y X es oxígeno.

11. Una composición farmacéutica compuesta de:

- una cantidad eficaz de agente inhibidor-PARP, seleccionado a partir de los compuestos definidos en la afirmación 1, o sales farmacéuticas o solvatos de los mismos;
- un portador farmacéuticamente aceptado para dicho agente inhibidor-PARP.

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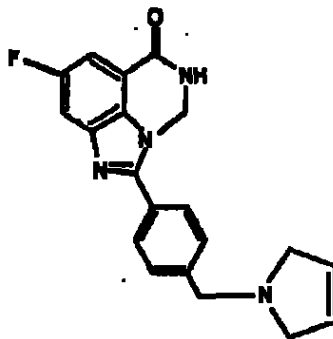
12. Un método para inhibir la actividad PARP de una enzima, que consta del contacto de la enzima con una cantidad efectiva de un compuesto tal como se define en la afirmación 1, o una sal farmacéuticamente aceptable o un solvato del mismo.

13. Un método de acuerdo a la afirmación 12, donde la enzima es poli-(ADP-ribosa) polimerasa o tanquirasa.

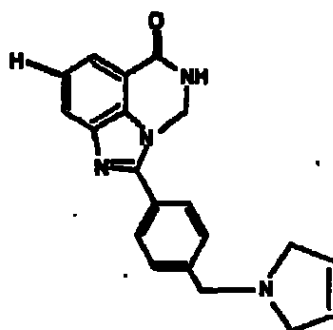
14. Un método para inhibir la actividad enzimática PARP en tejido mamífero que consiste en administrarle a un mamífero una cantidad terapéuticamente efectiva de un compuesto tal como se define en la afirmación 1, o una sal farmacéuticamente aceptable o un solvato del mismo.

15. Un método para inhibir la actividad enzimática PARP, que consta de contactar la enzima con una cantidad efectiva de un compuesto tal como se define en la afirmación 1, o una sal farmacéuticamente aceptable o un solvato del mismo.

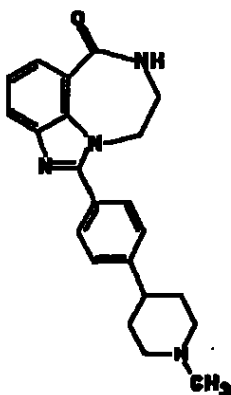
16. Un compuesto de la afirmación 1, el cual tienen la formula estructural:



17. Un compuesto de la afirmación 1, el cual tienen la formula estructural:



18. Un compuesto de la afirmación 1, el cual tienen la fórmula estructural:



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SUPERINDUSTRIA Y COMERCIO
Radicacion : 00065062 00000007 Folios: 13
Fecha (AM): 2006-01-13 17:56:03
Tramite : 002 PATENTES D 1 REGISTRAD/ 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 06 - 519
FECHA : ENERO 4 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	36765275	03/01/2006	2,943,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LENAS COMERCIALES	95,000.00
		TOTAL :	95,000.00

SON: NOVENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C., 21 de febrero de 2006

Apoderado: Carlos Reinaldo Olarte

Oficio: 2344

ASUNTO Radicación: 00-65062
 Trámite 002
 Evento 001
 Actuación 430
 Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

- ◆ capítulo descriptivo, folios 229 a 118;
- ◆ capítulo reivindicatorio modificado, folios 531 a 537;
- ◆ 1° examen de forma, folio 431;
- ◆ respuesta técnica al 1° examen de forma, folios 435 y 436;
- ◆ 2° examen de forma, folio 472;
- ◆ solicitud de la cual se reivindica prioridad y la traducción exigida, folios 16 a 228;
- ◆ solicitud del examen de patentabilidad, folios 475 y 476;
- ◆ examen de Art-46, folios 480 y 482;
- ◆ examen de patentabilidad Art-45, folios 478 y 479.
- ◆ anexos A – E, folios 485 a 525.

Objeto de la invención:

El título de la invención "LOS INHIBIDORES TRICICLICOS DE POLI (ADP-RIBOSA) POLIMERASAS".

Su objeto son los compuestos derivados de 2,3,6,7-tetrahidro-1H,5H-pirrolol[2,1-k][1,4]benzodiazepin-8(8aH)-ona; 2,3,6,7-tetrahidro-1H,5H-imidazo[5,1-k][1,4]benzodiazepin-8(8aH)-ona; 6,7-dihidro-1H,5H-imidazo[5,1-k][1,4]benzodiazepin-3,8(2H,8aH)-dione; 3-tioxo-2,3,6,7-tetrahidro-1H,5H-imidazo[5,1-k][1,4]benzodiazepin-8(8aH)-ona; 6,7-dihidro-1H,5H-imidazo[5,1-

k][1,4]benzodiazepina-3,8(2H,8aH)-diona y medicamentos que los comprenden como sustancia activa y sus sales fisiológicamente tolerables.

El campo de la invención, según la Clasificación Internacional de Patentes: A61K 31/551, 31/41

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Se realizó la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de la primera solicitud, de la cual se reivindica prioridad, 31 de agosto-1999. Consultada la fuente de información con que cuenta este despacho se encontró muchos documentos documentos solo se adjuntaron algunos:

No.	Documento No.	Título	*Fecha de Publicación
D1	W0 9713771	Bicyclic heteroaromatic compounds as protein tyrosine kinase Inhibitors	17-abril-1997
D2	US 3734919	4,5-di-hydropyrrolo[3,2,1-jk][1,4]benzodiazepine-7(6H)-ones and 4,5-di-hydropyrrolo[1,2,3-ef][1,5]benzodiazepine-6(7H)-ones	22-mayo-1973
D3	J. MED.CHEM	Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1.jk][1,4]benzodiazepin-2(1H)-one (TIBO)derivatives	1991

D4	J.MED.CHEM	Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) derivatives	1995
D5	J.MED.CHEM	Studies on the Imidazo[4,5,1-jk][1,4]benzodiazepine and imidazo[1,5,4-ef][1,5]benzodiazepine series	1978
D6	Chemical Abstract	Pyrolo[3,2,1-jk][1,4]benzodiazepin-1(2H)-one, 9chloro-3,4-dihydro-6,7-dimethyl.	1976
D7	Chimie thérapeutique	Sur quelques dérivatives de la phényl-1 méthyl-2 dihydro-4,5 6H-pyrrolo(3,2,1-ij)quinolénone-6	1973

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: ***"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."***

En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

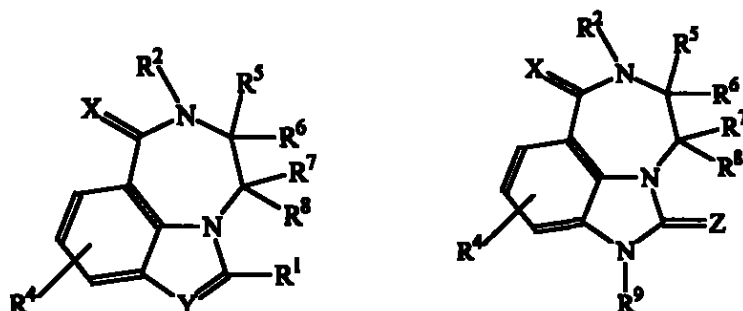
Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: ***"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica." "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."***

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha

de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

La solicitud en estudio reclama como nuevo derivados de las fórmulas:



-La anterioridad D1, comprende de compuestos derivados tienopirimidina y tienopiridina, especialmente los descritos en las paginas 20 a 23, los ejemplos 23 a 38, y además los compuestos específicos de los ejemplos, los intermedios específicos 4-clorotieno[3,2-d]pirimidina; 4-cloro-7-metiltieno[3,2-d]pirimidina; 4-cloro-5-etiltieno[3,2-d]pirimidina y 4-cloro-5-(2-tienil)tieno[3,2-d]pirimidina, son reclamados como nuevos en la solicitud en estudio, y por ser compuestos específicos destruyen categóricamente la novedad de los compuestos reclamados de forma general con las fórmulas arriba anotadas.

-La anterioridad D2 describe compuestos derivados de 4,5-dihidropirrol[3,2,jk][1,4]benzodiazepin-7(6H)-onas, con las fórmulas III, IIIa, V, especialmente; junto con la tabla 1, y los ejemplos de compuestos específicos de los ejemplos 3, 5, 14, 19; al igual que los procesos de síntesis y los medicamentos que los comprenden. Por lo cual se observa que la presente solicitud no tiene novedad ya que los compuestos se reclaman con formulas markush generales, mientras que la anterioridad es específica.

-D3 describe derivados 4,5,6,7-tetrahydro-5-metilimidazo[4,5,1-jk][1,4]benzodiazepina-2(1H)-ona (TIBO)derivados, especialmente el esquema IV^a, en los compuestos 24 y 25, son compuestos específicos que destruyen la novedad de la invención general reclamada con las formulas markush de la presente solicitud.

-D4 describe, la síntesis de derivados 4,5,6,7-tetrahidro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepina-2(1H)-ona, especialmente los compuestos de las formulas 1ax; 32^a,b; 1bf, bu, y que son compuestos que se califican como invención selectiva, respecto a la forma general de la solicitud en estudio, por lo tanto la solicitud en estudio se observa que no es nueva.

-D5 es el complemento de D4, ya que el interesado debía anexar el documento completo como se indica en el examen del Art-46 folio 418 y rehusó adjuntar completa solo anexo un solo folio de lo solicitado de cada artículo, al igual que D6, los cuales deben ser anexados por el interesado tal como se dice en el examen At-46.

-D7 se refiere a la síntesis de compuestos derivados de la fenil-1 metil-2 dihidro-4,5,6,7H-pirrol(3,2,1-ij)-6-quinoleína; especialmente los compuestos específicos con las fórmulas 6,7, 9, de la tabla 1; son compuestos específicos que destruyen la novedad de la invención general reclamada con las formulas Markush de la presente solicitud.

- Cuando se hagan las modificaciones se debe tener en cuenta que se conserve la unidad inventiva, puesto que los compuestos de la reivindicación 1, requieren búsqueda independiente de los de la reivindicación 9.

Cuando una solicitud está afectada su novedad, obviamente no posee nivel inventivo. En conclusión los requisitos de Patentabilidad de la presente solicitud están afectadas así:

Documento	Reivindicaciones	Requisito que afecta
D1	1 a 18	Novedad
D2	1 a 18	Novedad
D3	1 a 18	Novedad
D4	1 a 18	Novedad
D5	1 a 18	Novedad
D6	1 a 18	Novedad
D7	1 a 18	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
02 MAR 2006

CONCEPTO TÉCNICO No. 290	EXAMINADOR TÉCNICO Código No. 202012
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D 1

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 471/04, 495/04, A61K 31/505, C07D 491/048 // (C07D 471/04, 239:00, 221:00) (C07D 495/04, 333:00, 239:00)		A1	(11) International Publication Number: WO 97/13771 (43) International Publication Date: 17 April 1997 (17.04.97)						
(21) International Application Number: PCT/EP96/04399 (22) International Filing Date: 10 October 1996 (10.10.96) (30) Priority Data: <table><tr><td>9520845.0</td><td>11 October 1995 (11.10.95)</td><td>GB</td></tr><tr><td>9614757.4</td><td>13 July 1996 (13.07.96)</td><td>GB</td></tr></table> (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Bertsley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): COCKERILL, George, Stuart [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). GUNTRIP, Stephen, Barry [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). McKEOWN, Stephen, Carl [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). PAGE, Martin, John [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). SMITH, Kathryn, Jane [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). VILE, Sadie [GB/GB]; Glaxo Wellcome plc,		9520845.0	11 October 1995 (11.10.95)	GB	9614757.4	13 July 1996 (13.07.96)	GB	Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HUDSON, Alan, Thomas [GB/GB]; Long Lodge Cottage, Oxford, Kent TN14 5RH (GB). BARRACLOUGH, Paul [GB/GB]; 27 Sevington Park, Loose, Near Maldstone, Kent ME15 9SB (GB). FRANZMANN, Karl, Witold [GB/GB]; 6 Northstead Road, Tulse Hill, London SW2 3JW (GB). (74) Agent: REED, Michael, A.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
9520845.0	11 October 1995 (11.10.95)	GB							
9614757.4	13 July 1996 (13.07.96)	GB							
(54) Title: BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS									
(57) Abstract Substituted heteroaromatic compounds of formula (A) wherein X is N or CH; in which (a) represents a fused 5, 6 or 7-membered heterocyclic ring and R³ is a group ZR⁴ wherein Z is joined to R⁴ through a (CH₂)_p group in which p is 0, 1, or 2 and Z represents a group V(CH₂), V(CF₂), (CH₂)V, (CF₂)V, V(CRR'), V(CHR) or V where R and R' are each C₁₋₄ alkyl and in which V is a hydrocarbyl group containing 0, 1 or 2 carbon atoms, carbonyl, dicarbonyl, CH(OH), CH(CN), sulphonamide, amide, O, S(O)_m or NR^b where R^b is hydrogen or R^b is C₁₋₄ alkyl; and R⁴ is an optionally substituted C₃₋₆ cycloalkyl or an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety; or R³ is a group ZR⁴ in which Z is NR^b, and NR^b and R⁴ together form an optionally substituted 5, 6, 7, 8, 9 or 10-membered carbocyclic or heterocyclic moiety, are protein tyrosine kinase inhibitors. The compounds are described, as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of psoriasis, fibrosis, atherosclerosis, restenosis, auto-immune disease, allergy, asthma, transplantation rejection, inflammation, thrombosis, nervous system diseases, and cancer.									
(A) (a)									

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A further aspect of the invention provides a method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity which comprises administering to the human or animal subject an effective amount of a compound of formula (A) or a pharmaceutically acceptable salt thereof.

A further aspect of the present invention provides the use of a compound of formula (A), or a pharmaceutically acceptable salt thereof, in therapy.

A further aspect of the present invention provides the use of a compound of formula (A), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of malignant tumours.

A further aspect of the present invention provides the use of a compound of formula (A), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of atherosclerosis, restenosis or thrombosis.

Whilst it is possible for the compounds or salts of the present invention to be administered as the new chemical, it is preferred to present them in the form of a pharmaceutical formulation.

According to a further feature of the present invention we provide pharmaceutical formulations comprising at least one compound of the formula (A), or pharmaceutically acceptable salt(s) thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain for example 0.5mg to 1g, preferably 5mg to 100mg of a compound of the formula (A) depending on the condition being treated, the route of administration and the age, weight and condition of the patient.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such

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formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds of the formula (A) and salts thereof have anticancer activity as demonstrated hereinafter by their inhibition of the protein tyrosine kinase c-erbB-2 enzyme. It has thus been established that compounds of the present invention are of use in medicine and, in particular in the treatment of certain human malignancies, for example breast, ovarian non-small cell lung, pancreatic, gastric and colon cancers. Accordingly, the present invention provides a method for the treatment of susceptible malignancies in an animal, e.g. a human, which comprises administering to the animal a therapeutically effective amount of a compound or salt of the present invention. In the alternative, there is also provided a compound or salt of the present invention for use in medicine and, in particular, for use in the treatment of cancers.

The present invention also provides the use of a compound of formula (A) or a salt thereof for the manufacture of a medicament for treatment of malignant tumours.

The animal requiring treatment with a compound or salt of the present invention is usually a mammal, such as a human being.

A therapeutically effective amount of a compound or salt of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of the present invention for the treatment of neoplastic growth, for example colon or breast carcinoma will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt of the present invention may be determined as a proportion of the effective amount of the compound per se.

toluene to remove the excess thionyl chloride, to give 6-benzyloxy-4-chloropyrido[3,4-d]pyrimidine; δH [$^2\text{H}_6$]-DMSO 8.73 (1H,s), 8.10 (1H,s), 7.25-7.55 (6H,m), 5.41 (2H,s).

Benzyloxy-4-chloropyrido[3,4-d]pyrimidine (ca. half the above material, ca. 2 mmol) was reacted with 4-benzyloxyaniline (0.430g, 2.25 mmol) in acetonitrile (10ml) according to Procedure A for 5 hours. The resulting brown solid was 6-benzyloxy-4-(4-benzyloxyanilino)pyrido[3,4-d]pyrimidine (0.621g, 71%); δH [$^2\text{H}_6$]-DMSO 8.99 (1H,s), 8.73 (1H,s), 8.22 (1H,s), 7.71 (2H,d), 7.15-7.55 (10H,m), 7.10 (2H,d), 5.50 (2H,s), 5.13 (2H, s); m/z ($M + 1$)⁺ 435.

Example 22

4-(4-Benzyloxyanilino)pyrido[2,3-d]pyrimidine

4-Chloropyrido[2,3-d]pyrimidine (prepared as described in: R.K. Robins and G.W. Hitchings, *J. Am. Chem. Soc.*, **77**, 2256 (1955)) (0.165g, 1.0 mmol) and 4-benzyloxyaniline (0.199g, 1.0 mmol) were reacted in ethanol (10 ml) for ca. 2 hours, according to Procedure A. After cooling, the mixture was filtered, treated with triethylamine and concentrated *in vacuo*. Purification by column chromatography on silica, eluting with methanol/chloroform (1:10), gave the product as a yellow solid (0.020g, 6%) with m.p. 235-237°C; (Found: C, 72.34; H, 4.85; N, 16.57. $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O} \cdot 0.25\text{H}_2\text{O}$ requires: C, 72.16; H, 4.99; N, 16.83%); δH [$^2\text{H}_6$]-DMSO 9.10 (1H, d, J 9) and 9.08 (1H, d, J 5) (6H, 8-H), 8.78 (1H, s, 2-H), 7.76 (1H, dd, J 9, 5, 7-H), 7.62 (2H, d, J 9, 2'-H, 6'-H), 7.43 (2H, d, J 7, 2''-H, 6''-H), 7.38 (2H, t, J 7, 3''-H, 5''-H), 7.30 (1H, t, J 8, 4''-H), 7.08 (2H, d, J 9, 3'-H, 5'-H), 5.11 (2H, s, CH_2); m/z (%) 328 (68, M^+), 237 (100), 91 (64).

Example 23

4-(4-Benzyloxyanilino)thieno[3,2-d]pyrimidine hydrochloride

4-Chlorothieno[3,2-d]pyrimidine (commercially available from Maybridge Chemical Co. Ltd.) (0.400g, 2.35 mmol) and 4-benzyloxyaniline (0.514g, 2.50 mmol) were reacted in 2-propanol (10 ml) for 2.5 hours, according to Procedure A. The product was obtained as pale cream prisms (0.640g, 74%) with m.p. 227-229°C; (Found: C, 60.86; H, 4.19; N, 11.31. $\text{C}_{19}\text{H}_{15}\text{N}_3\text{OS} \cdot \text{HCl} \cdot 0.33\text{H}_2\text{O}$ requires: C, 60.71; H, 4.43; N, 11.19%); tlc (ethyl acetate) R_f 0.38; δH [$^2\text{H}_6$]-DMSO 11.32 (1H, br s, NH), 8.81 (1H, s, 2-H), 8.45 (1H, d, J 7, 6 H or 7 H) 7.28-7.62 (6H, m, 6H or 7H, 2'-H, 6'-H, 5 x PhH), 7.10

559
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(2H, d, J 9, 3'-H, 5'-H), 5.15 (2H, s, CH₂); m/z (%) 333 (34, M⁺), 242 (100), 91 (49).

Example 24

4-[3-Chloro-4-(2-methoxybenzyloxy)anilino]thieno[3,2-d]pyrimidine hydrochloride

4-Chlorothieno[3,2-d]pyrimidine (0.102g, 0.60 mmol) and 3-chloro-4-(2-methoxybenzyloxy)aniline (prepared according to the published method: WO 96/09294) (0.161g, 0.65 mmol) were reacted in 2-propanol (4 ml) for 1.25 hours, according to Procedure A. The product was obtained as pale cream prisms (0.203g, 78%) with m.p. 210-212°C; (Found: C, 55.28; H, 4.00; N, 9.44. C₂₀H₁₆ClN₃O₂S.HCl requires: C, 55.31; H, 3.92; N, 9.67%); δ H [²H₆]-DMSO 11.19 (1H, br s, NH), 8.88 (1H, s, 2-H), 8.48 (1H, d, J 7, 6 H or 7 H) 7.87 (1H, d, J 5, 2'-H), 7.55-7.62 (2H, m, 6'-H, 4''-H), 7.48 (1H, d, J 7, 6H or 7H), 7.28-7.40 (2H, m, 5'-H, 6''-H), 7.09 (1H, d, J 9, 3''-H), 7.00 (1H, t, J 9, 5''-H), 5.22 (2H, s, CH₂), 3.85 (3H, s, OCH₃).

Example 25

4-[3-Chloro-4-(2-fluorobenzyloxy)anilino]thieno[3,2-d]pyrimidine hydrochloride
4-Chlorothieno[3,2-d]pyrimidine (0.103g, 0.60 mmol) and 3-chloro-4-(2-fluorobenzyloxy)aniline (prepared according to the published method: WO 96/09294) (0.197g, 0.78 mmol) were reacted in 2-propanol (4.5ml) for 4.5 hours, according to Procedure A. The product was obtained as cream prisms (0.208g, 82%) with m.p. 231-233°C; (Found: C, 53.39; H, 3.30; N, 9.79. C₁₉H₁₃ClF₂N₃OS.HCl.H₂O requires: C, 53.47; H, 3.42; N, 9.85%); δ H [²H₆]-DMSO 8.88 (1H, s, 2-H), 8.47 (1H, d, J 7, 6 H or 7 H) 7.88 (1H, d, J 5, 2'-H), 7.55-7.68 (3H, m), 7.33-7.49 (2H, m), 7.20-7.30 (2H, m) (6H or 7H, 5'-H, 6'-H, 3''-H, 4''-H, 5''-H, 6''-H), 5.29 (2H, s, CH₂); m/z 385 (M+1⁺).

Example 26

4-[4-(2-Bromobenzyloxy)-3-chloroanilino]thieno[3,2-d]pyrimidine hydrochloride

4-Chlorothieno[3,2-d]pyrimidine (0.103g, 0.60 mmol) and 4-(2-fluorobenzyloxy)-3-chloroaniline (prepared according to the published method: WO 96/09294) (0.234g, 0.75 mmol) were reacted in 2-propanol (5ml) according to Procedure A. The product was obtained as pale cream prisms

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(0.256g, 88%) with m.p. 247-248°C; (Found: C, 47.10; H, 2.91; N, 9.03. $C_{19}H_{13}BrClN_3OS.HCl$ requires: C, 47.23; H, 2.92; N, 8.70%); δH [$^2H_6$]-DMSO 11.28 (1H, br s, N-H), 8.88 (1H, s, 2-H), 8.49 (1H, d, J 7, 6 H or 7 H) 7.89 (1H, d, J 5, 2'-H), 7.57-7.75 (4H, m), 7.44-7.53 (1H, m), 7.30-7.39 (2H, m) (6H or 7H, 5'-H, 6'-H, 3''-H, 4''-H, 5''-H, 6''-H), 5.29 (2H, s, CH_2); m/z 447 (M^+).

Example 27

4-[3-Methoxy-4-(2-methoxybenzyloxy)anilino]thieno[3,2-d]pyrimidine hydrochloride

4-Chlorothieno[3,2-d]pyrimidine (0.102g, 0.60 mmol) and 3-methoxy-4-(2-methoxybenzyloxy)aniline (prepared according to the published method: WO 96/09294) (0.181g, 0.70 mmol) were reacted in 2-propanol (3ml) for 75 minutes according to Procedure A. The product was obtained as off-white prisms (0.211g, 82%) with m.p. 207-208°C; (Found: C, 58.55; H, 4.76; N, 9.53. $C_{21}H_{19}N_3O_3S.HCl$ requires: C, 58.55; H, 4.69; N, 9.77%); δH [$^2H_6$]-DMSO 8.85 (1H, s, 2-H), 8.41 (1H, d, J 7, 6 H or 7 H) 7.55 (1H, d, J 7, 6-H or 7-H), 7.42 (1H, d, J 9, 6'-H), 7.34 (1H, t, J 8, 4''-H), 7.29 (1H, s, 2'-H), 7.02-7.20 (3H, m, 5'-H, 3''-H, 6''-H), 6.98 (1H, t, J 8, 5''-H), 5.08 (2H, s, CH_2), 3.83 and 3.79 (2 x 3H, 2 x s, 2 x OCH_3); m/z 393 (M^+).

Example 28

4-(4-Benzylanilino)thieno[3,2-d]pyrimidine hydrochloride

4-Chlorothieno[3,2-d]pyrimidine (0.080g, 0.35 mmol) and 4-aminodiphenylmethane (commercially available from K & K) (0.080g, 0.44 mmol) were reacted in 2-propanol (5 ml) for 30 minutes according to Procedure A. The white solid obtained was 4-(4-benzylanilino)thieno[3,2-d]pyrimidine hydrochloride (0.070g, 56%), m.p. 251-255°C; (Found: C, 64.00; H, 4.45, N, 11.72. $C_{19}H_{15}N_3S.HCl.0.1H_2O$ requires: C, 64.16; H, 4.59; N, 11.81%); δH [$^2H_6$]-DMSO 11.05 (1H, br s, NH), 8.81 (1H, s, 2-H), 8.43 (1H, d, J 8, 6-H or 7-H), 7.60-7.52 (3H, m, (6-H or 7-H), 2'-H, 6'-H), 7.35-7.20 (6H, m, 3'-H, 5'-H, 2''-H, 3''-H, 5''-H, 6''-H), 7.19 (1H, t, J 6, 4''-H), 3.95, (2H, s, CH_2); m/z (%) 318 (100, $M+1^+$); n_{max} (KBr disc)/ cm^{-1} 2570, 1630, 1595, 1485, 1475, 1365.

553
546**Example 29****4-(4-Phenoxyvanilino)thieno[3,2-d]pyrimidine hydrochloride**

4-Chloro[thieno[3,2-d]pyrimidine (0.085g, 0.50 mmol) and 4-phenoxyaniline (0.105g, 0.55 mmol) were reacted in 2-propanol (3.5 ml) for 3 hours according to Procedure A. The product was obtained as a cream solid (0.130g, 73%), m.p. 236-240°C; (Found: C, 60.61; H, 3.95, N, 11.93. C₁₈H₁₃N₃OS.HCl requires: C, 60.76; H, 3.97; N, 11.81%); δ H [²H₅]-DMSO 10.93 (1H, br s, NH), 8.80 (1H, s, 2-H), 8.42 (1H, d, J 8, 6-H or 7-H), 7.69 (2H, d, J 9, 2'-H, 6'-H), 7.55 (1H, d, J 8, 6-H or 7-H), 7.41 (2H, t, J 9, 3''-H, 5''-H), 7.18 (1H, t, J 9, 4''-H), 7.04-7.15 (4H, m, 3'-H, 5'-H, 2''-H, 6''-H); m/z (%) 318 (100, M-1⁺).

Example 30**4-(4-(a,a-Difluorobenzoyloxy)anilino)thieno[3,2-d]pyrimidine hydrochloride**

A mixture of 1,3 dibromo-5,5-dimethylhydantoin (11.5g, 40.2 mmol), a,a-difluorotoluene (prepared by the published method of W. J. Middleton, *J. Org. Chem.*, 1975, 40, p574) (7.0g, 55 mmol) and AIBN (0.25g) in CCl₄ (300ml) was heated at reflux for 10 h while being irradiated (tungsten filament lamp, 500W). The mixture was then diluted with petrol and the remaining precipitate removed by filtration. The filtrate was then evaporated and the resulting oil chromatographed (silica, petrol) to give a-bromo-a, a-difluorotoluene (5.5g, 50%) as a colourless oil; δ H [²H₅]-DMSO 7.68 (2H, d, J 8, 2-H, 6-H), 7.62-7.55 (3H, m, 3-H, 4-H, 5-H); dC [²H₃]-CDCl₃ 138.3 (triplet, J 23, 1-C), 131.2 (4-C), 128.6 (3-C and 5-C), 124.3 (2-C and 6-C), 118.6 (triplet, J 300, CBrF₂). This ¹³C data agrees with that published by A. Haas *et al.*, *Chem Ber.*, 1988, 121, p1329.

4-Nitrophenol (16.6g, 0.119 mol) was added to a stirred solution of potassium hydroxide (7.0g, 0.13 g) in absolute ethanol (50ml) and the mixture was heated at reflux for 30 min. Diethyl ether was then added to this yellow mixture and the resulting yellow precipitate collected by filtration to give potassium 4-nitrophenoxide (19.5g, 93%) as a bright yellow solid, which was used directly in the next step.

A stirred mixture of potassium 4-nitrophenoxide (5.47g, 31mmol) and a-bromo-a,a-difluorotoluene (3.2g, 15 mmol) in dry DMF (30 ml) under N₂ was heated at 78-80°C for 8 h. The mixture was then concentrated *in vacuo* to remove most of the DMF, and the residue was partitioned between aq. sat. sodium bicarbonate (30ml) and dichloromethane. The organic layer was separated

and the water layer further extracted with dichloromethane (2 x 50ml). The combined organics were washed with water and dried over Na_2SO_4 . The solvents were then evaporated *in vacuo* and the residue chromatographed (silica, 10% diethyl ether/petrol) to give 4-(a,a-difluorobenzyloxy)nitrobenzene (2.7g, 67%) as a white crystalline solid, m.p. 46-48°C; δH [$^2\text{H}_6$]-DMSO 8.80 (2H, d, J 9, 2-H, 6-H), 7.78 (2H, d, J 9, 2'-H, 6'-H), 7.65-7.55 (5H, m, 3-H, 5-H, 3'-H, 4'-H, 5'-H); m/z (%) 285 (39, M^+), 246 (44), 127 (100).

A solution of 4-(a,a-difluorobenzyloxy)nitrobenzene (0.65g, 2.5 mmol) in a mixture of ethyl acetate (25ml) and methanol (25ml) was carefully added to 10% palladium on charcoal (50mg). The resulting suspension was stirred at r.t.p. under an atmosphere of hydrogen. When the reaction was complete (as indicated by tic and calculated uptake of hydrogen) the suspension was filtered through a pad of hyflo and the filtrate evaporated to dryness to give 4-(a,a-difluorobenzyloxy)aniline (0.56g, 98%) as an off-white solid; δH [$^2\text{H}_6$]-DMSO 7.75 (2H, d, J 7, 2'-H, 6'-H), 7.62 (3H, m, 3'-H, 4'-H, 5'-H), 7.00 (2H, d, J 7, 2-H, 6-H), 6.60 (2H, d, J 7, 3-H, 5-H), 5.10 (2H, br s, NH_2); m/z (%) 235 (95, M^+), 127 (100).

4-Chlorothieno[3,2-d]pyrimidine (0.049g, 0.29 mmol) and 4-(a,a-difluorobenzyloxy)aniline (0.085g, 0.36 mmol) were reacted in 2-propanol (5ml) for 30 minutes according to Procedure A. The white solid obtained was 4-(4-(a,a-difluorobenzyloxy)anilino)thieno[3,2-d]pyrimidine hydrochloride (0.053g, 36%), m.p. 265°C (dec); (Found: C, 56.57; H, 3.47, N, 10.42. $\text{C}_{19}\text{H}_{13}\text{N}_3\text{SOF}_2\cdot\text{HCl}$ requires: C, 56.23; H, 3.48; N, 10.35%); δH [$^2\text{H}_6$]-DMSO 11.25 (1H, br s, NH), 8.88 (1H, s, 2-H), 8.50 (1H, d, J 5, 6-H or 7-H), 7.80-7.73 (4H, m, 2'-H, 6'-H, 2''-H, 6''-H); 7.67-7.55 (4H, m, 3''-H, 4''-H, 5''-H and (6-H or 7-H)), 7.40 (2H, d, J 9, 3'-H, 5'-H); m/z (%) 369 (60, M^+), 242 (100); ν_{max} (KBr disc)/ cm^{-1} 2550, 1630, 1591, 1504, 1468, 1321.

Example 31

4-[4-(2-Thienylmethoxy)anilino]thieno[3,2-d]pyrimidine hydrochloride

4-Chlorothieno[3,2-d]pyrimidine (0.102g, 0.60 mmol) and 4-(2-thienylmethoxy)-aniline (prepared according to the published method: WO 96/09294) (0.135g, 0.66 mmol) were reacted in 2-propanol (5 ml) for 2 hours, according to Procedure A. The product was obtained as a grey-green solid (0.138g, 61%) with m.p. 181-182°C; (Found: C, 53.64; H, 3.61; N, 11.04. $\text{C}_{17}\text{H}_{13}\text{N}_3\text{OS}_2\cdot\text{HCl}\cdot 0.25\text{H}_2\text{O}$ requires: C, 53.68; H, 3.84; N, 11.05%); δH [$^2\text{H}_6$]-

DMSO 11.28 (1H, br s, NH), 8.75 (1H, s, 2-H), 8.45 (1H, d, J 7, 6 H or 7 H) 7.45-7.68 (4H, m, 6H or 7H, 2'-H, 6'-H, 5''-H), 6.95-7.28 (4H, m, 3'-H, 5'-H, 3''-H, 4''-H), 5.32 (2H, s, CH₂); m/z 339 (M⁺).

Example 32

4-(4-Cyclohexylmethoxyvanilino)thieno[3,2-d]pyrimidine hydrochloride

4-Chlorothieno[3,2-d]pyrimidine (0.171g, 1.00 mmol) and 4-cyclohexylmethoxy-aniline (prepared according to the published method: WO 96/09294) (0.205g, 1.00 mmol) were reacted in 2-propanol (5 ml) for 5 hours, according to Procedure A. The product was obtained as cream prisms (0.255g, 68%) with m.p. 232-233°C; (Found: C, 60.65; H, 5.68; N, 11.25. C₁₈H₂₁N₃OS.HCl requires: C, 60.71; H, 5.90; N, 11.23%); δ H [²H₅]-DMSO 11.11 (1H, br s, NH), 8.71 (1H, s, 2-H), 8.41 (1H, d, J 7, 6 H or 7 H) 7.44-7.58 (3H, m, 6H or 7H, 2'-H, 6'-H), 7.03 (2H, d, J 9, 3'-H, 5'-H), 3.84 (2H, s, CH₂), 1.58-1.90 (6H, m) and 0.98-1.33 (5H, m) (cyclohexyl-H₁₁); m/z 339 (M⁺).

Example 33

7-Methyl-4-(4-phenoxyvanilino)thieno[3,2-d]pyrimidine hydrochloride

4-Chloro-7-methylthieno[3,2-d]pyrimidine (commercially available from Maybridge Chemical Co. Ltd.) (0.185g, 1.00 mmol) and 4-phenoxyaniline (0.210g, 1.1 mmol) were reacted in 2-propanol (5 ml) for 2 hours according to Procedure A. The product was obtained as a yellow solid (0.294g, 80%), m.p. 243-245°C; (Found: C, 61.46; H, 4.27, N, 11.32. C₁₈H₁₅N₃OS.HCl requires: C, 61.70; H, 4.36; N, 11.36%); δ H [²H₅]-DMSO 10.85 (1H, br s, NH), 8.78 (1H, s, 2-H), 8.05 (1H, t, 6-H), 7.69 (2H, d, J 9, 2'-H, 6'-H), 7.42 (2H, t, J 9, 3''-H, 5''-H), 7.00-7.20 (5H, m, 3'-H, 5'-H, 2''-H, 4''-H, 6''-H), 2.43 (3H, s, 7-CH₃); m/z (%) 333 (M⁺).

Example 34

4-(4-Benzoyloxy-3-trifluoromethylanilino)-7-methylthieno[3,2-d]pyrimidine hydrochloride

4-Chloro-7-methylthieno[3,2-d]pyrimidine (0.111g, 0.60 mmol) and 4-benzoyloxy-3-trifluoromethylaniline (prepared according to the published method: WO 96/09294) (0.194g, 0.78 mmol) were reacted in 2-propanol (4.5 ml) for 4 hours according to Procedure A. The product was obtained as a pale pink solid (0.257g, 95%), m.p. 219-220°C; (Found: C, 56.30; H, 4.91, N,

8.21. $C_{21}H_{18}F_3N_3OS.HCl.iPrOH$ requires: C, 56.30; H, 4.89; N, 8.21%; δH [$^2H_6$]-DMSO 11.12 (1H, br s, NH), 8.81 (1H, s, 2-H), 8.12 (1H, s, 6-H), 8.02 (1H, d, J 2, 2'-H), 7.97 (1H, dd, J 9,2, 6'-H), 7.29-7.49 (6H, m, 5'-H, PhH_s), 5.32 (2H, s, CH_2), 5.79 (1H, sept, J 6, $CHOH$ of $iPrOH$), 2.45 (3H, s, 7- CH_3), 1.05 (6H, d, J 6, $C(CH_3)_2$ of $iPrOH$); m/z (%) 415 (M^+).

Example 35

4-[3-Chloro-4-(2-fluorobenzyloxy)anilino]-5-methylthieno[2,3-d]pyrimidine hydrochloride

4-Chloro-5-methylthieno[2,3-d]pyrimidine (commercially available from Maybridge Chemical Co. Ltd.) (0.092g, 0.50 mmol) and 3-chloro-4-(2-fluorobenzyloxy)aniline (prepared according to the published method: WO 96/09294) (0.164g, 0.65 mmol) were reacted in 2-propanol (3.5ml) for 4 hours, according to Procedure A. The product was obtained as cream plates (0.156g, 72%) with m.p. 193-196°C; (Found: C, 55.17; H, 3.77; N, 9.56. $C_{20}H_{15}ClFN_3OS.HCl$ requires: C, 55.05; H, 3.70; N, 9.63%); δH [$^2H_6$]-DMSO 8.39 (1H, s, 2-H), 8.37 (1H, br s, N-H), 7.75 (1H, d, J 4, 2'-H), 7.49-7.59 (2H, m), 7.34-7.44 (1H, m), 7.15-7.32 (4H, m) (6-H, 5'-H, 6'-H, 3"-H, 4"-H, 5"-H, 6"-H), 5.19 (2H, s, CH_2), 2.69 (3H, s, 5- CH_3); m/z 400 ($M+1^+$).

Example 36

4-(4-Cyclohexylmethoxyvanilino)-5-methylthieno[2,3-d]pyrimidine hydrochloride

4-Chloro-5-methylthieno[2,3-d]pyrimidine (0.092g, 0.50 mmol) 4-cyclohexylmethoxyaniline (prepared according to the published method: WO 96/09294) (0.133g, 0.65 mmol) were reacted in 2-propanol (3.5 ml) for 8 hours according to Procedure A. The product was obtained as a colourless solid (0.120g, 62%), m.p. 180-183°C; (Found: C, 60.83; H, 6.10, N, 10.53. $C_{26}H_{23}N_3OS.HCl.0.25H_2O$ requires: C, 60.90; H, 6.22; N, 10.65%); δH [$^2H_6$]-DMSO 8.48 (1H, br s, NH), 8.39 (1H, s, 2-H), 7.50 (2H, d, J 9, 2'-H, 6'-H), 7.31 (1H, s, 6-H), 6.97 (2H, d, J 9, 3'-H, 5'-H), 3.81 (2H, d, J 8, CH_2), 2.73 (3H, s, 5- CH_3), 1.60-1.88 (6H, m) and 0.98-1.45 (5H, m) (cyclohexyl- H_{11}); m/z 354 ($M+1^+$).

Example 37 ✓**5-Methyl-4-(4-phenoxyanilino)thieno[2,3-d]pyrimidine hydrochloride**

4-Chloro-5-methylthieno[2,3-d]pyrimidine (0.185g, 1.00 mmol) and 4-phenoxyaniline (0.210g, 1.1 mmol) were reacted in 2-propanol (6 ml) for 17 hours according to Procedure A. The product was obtained as a pale grey solid (0.297g, 80%), m.p. 218-221°C; (Found: C, 61.61; H, 4.33, N, 11.25. $C_{19}H_{15}N_3OS \cdot HCl$ requires: C, 61.70; H, 4.36; N, 11.36%); δH [$^2H_6$]-DMSO 8.60 (1H, br s, NH), 8.49 (1H, s, 2-H), 7.68 (2H, d, J 9, 2'-H, 6'-H), 7.33-7.48 (3H, m, 6-H, 3''-H, 5''-H), 7.17 (1H, t, J 9, 4''-H), 7.00-7.10 (4H, m, 3'-H, 5'-H, 2''-H, 6''-H), 2.75 (3H, s, 5-CH₃); m/z 333 (M^+).

Example 38 ✓**4-(4-Phenoxyanilino)-5-(2-thienyl)thieno[2,3-d]pyrimidine hydrochloride**

4-Chloro-5-(2-thienyl)thieno[2,3-d]pyrimidine (commercially available from Maybridge Chemical Co. Ltd.) (0.126g, 0.50 mmol) and 4-phenoxyaniline (0.116g, 0.63 mmol) were reacted in 2-propanol (3 ml) for 6.5 hours according to Procedure A. The product was obtained as an off-white powder (0.150g, 71%), m.p. 171-172°C (effervescence); (Found: C, 62.60; H, 3.60, N, 9.85. $C_{22}H_{15}N_3OS_2 \cdot 0.67HCl$ requires: C, 62.06; H, 3.71; N, 9.87%); δH [$^2H_6$]-DMSO 8.58 (1H,s), 7.79-7.85 (2H,m), 7.29-7.56 (7H,m), 6.93-7.13 (5H,m); m/z 401 (M^+).

Example 39**4-(4-Benzoyloxy-3-chloroanilino)-6-(N,N-dimethylamino)pyrido[3,4-d]pyrimidine hydrochloride.**

Prepared according to Procedure A from 4-chloro-6-(N,N-dimethylamino)-pyrido[3,4-d]pyrimidine and 4-benzoyloxy-3-chloroaniline (prepared according to the published method: WO96/09294); tlc (dichloromethane: ethanol: aq. ammonia, 100:8:1) R_f 0.48; m/z ($M + 1$)⁺ 406.

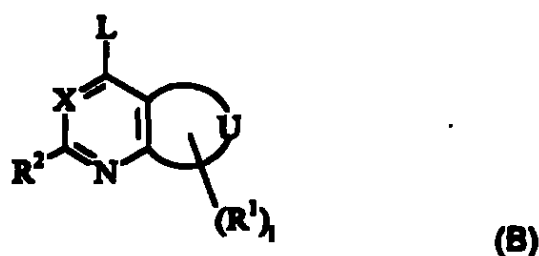
Table 1

Compound of Example	erbB-2 Substrate Phosphorylation	HB4a erbB-2 Cell Proliferation	HB4a ras Cell Proliferation
1	58	2700	17000
2	26	690	3700
3	115	11000	44000
4	124	2500	11000
5	14	500	11000
7	1.3	300	>50000
8	20	590	7500
11	920	10000	37000
12	24	1600	31000
14	900	15000	50000
15	30	570	32000
16	50	2400	6600
17	200	4400	10000
18	5	150	28000
20	10	2400	46000
23	300	2000	5000
24	50	10000	18000
25	150	500	3000
26	230	2500	30000
28	200	3000	13000
29	110	5000	20000
30	860	6000	15000
35	99	8000	25000
36	500	10000	10000
37	650	17000	25000
38	490	20000	20000

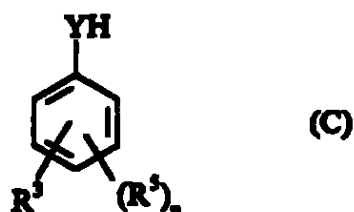
15. A pharmaceutical formulation comprising one or more compounds of formula (A), or pharmaceutically acceptable salt(s) thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

16. A pharmaceutical formulation as claimed in claim 15 in unit dosage form and containing a compound of formula (A) or a pharmaceutically acceptable salt thereof in an amount from 70 to 700 mg.

17. A process for the preparation of a compound of formula (A), comprising the reaction of a compound of formula (B):



with a compound of the formula C:



wherein L is a suitable leaving group and X, Y, I, n and R¹ to R⁵ are as defined in claim 1.

18. A process as claimed in claim 17 wherein the process also includes the step of converting one compound of formula (B) into another compound of formula (B) prior to the reaction with the compound of formula (C).

19. A process as claimed in claim 17 or claim 18 wherein the process also includes the step of converting one compound of formula (C) into another compound of formula (C) prior to the reaction with the compound of formula (B).

20. A process as claimed in any one of claims 17 to 19, the process also including the step of converting one compound of formula (A) into another compound of formula (A).
21. A compound of formula (A), or a pharmaceutically acceptable salt thereof, for use in therapy.
22. Use of a compound of formula (A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder mediated by aberrant tyrosine kinase activity.
23. Use of a compound of formula (A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of malignant tumours.
24. Use of a compound of formula (A), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of atherosclerosis, restenosis or thrombosis.
25. A method of treatment of a human or animal subject suffering from a disorder mediated by aberrant tyrosine kinase activity which comprises administering to the human or animal subject an effective amount of a compound of formula (A) or a pharmaceutically acceptable salt thereof.

United States Patent Office

3,734,919

Patented May 22, 1973

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3,734,919

4,5 - DI-HYDROPYRROLO[3,2,1-jk][1,4]BENZODIAZEPIN-7(6H)-ONES AND 4,5-DI-HYDROPYRROLO[1,2,3-ef][1,5]BENZODIAZEPIN-6(7H)-ONES

Jackson B. Hester, Jr., Portage, Mich., assignor to The Upjohn Company, Kalamazoo, Mich.

No Drawing. Original application Nov. 3, 1969, Ser. No. 873,693, now Patent No. 3,642,821. Divided and this application June 21, 1971, Ser. No. 155,282
Int. Cl. C07d 53/02

U.S. Cl. 268-239.3 T

14 Claims

ABSTRACT OF THE DISCLOSURE

4,5,6,7 - tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepines, 4,5,6,7 - tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepines, 4,5 - dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-ones, 4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-ones and processes for preparing the same. Said compounds exhibit tranquilizing and anti-convulsant activity.

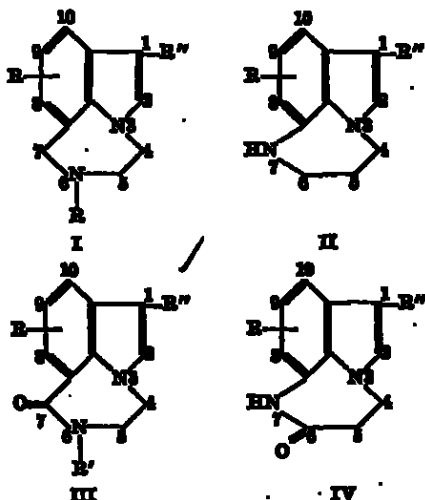
BRIEF SUMMARY OF THE INVENTION

This is a division of application Ser. No. 873,693, filed Nov. 3, 1969, now U.S. Pat. No. 3,642,821. This invention relates to novel

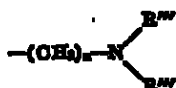
4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepines (I),
4,5,6,7-tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepines (II),
4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-ones (III),
4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-ones (IV) and

processes for preparing the same.

The novel compounds of this invention have the formulae

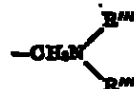


wherein R is selected from the group consisting of hydrogen, alkyl of from 1 to 3 carbon atoms, inclusive, alkoxy of from 1 to 3 carbon atoms, inclusive, and halogen; wherein R' is selected from the group consisting of hydrogen, alkyl of from 1 to 3 carbon atoms, inclusive, 4-oxo-4-(p-fluorophenyl)butyl, and the group



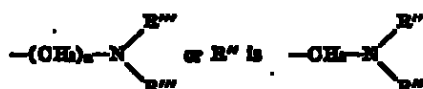
wherein n is an integer of from 2 to 4, inclusive, and R'''

is alkyl of from 1 to 3 carbon atoms, inclusive; and wherein R'' is hydrogen or the group



wherein R''' is the same as above.

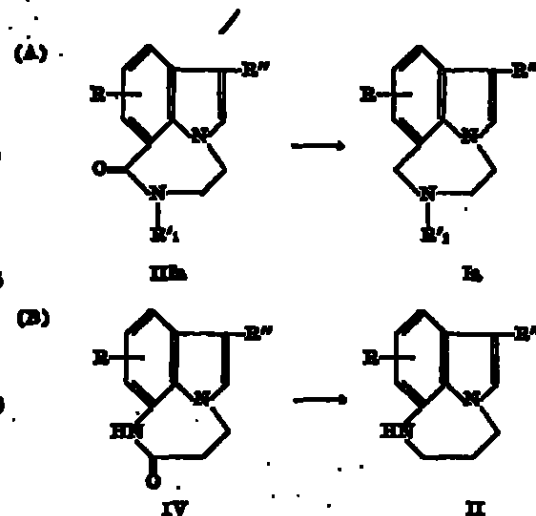
The term "novel compounds of this invention," as used throughout the specification embraces the compounds represented by Formulas I, II, III and IV above, and the acid addition salts of (a) the compounds represented by Formulas I and II and (b) the compounds represented by Formulas III and IV wherein R' is



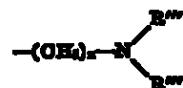
as defined above.

The term halogen is inclusive of chlorine, bromine and fluorine.

The compounds of Formula I, except those compounds of Formula I wherein R' is 4-oxo-4-(p-fluorophenyl)butyl can be prepared by reducing the corresponding compounds of Formula III and the compounds of Formula II can be prepared by reducing the compounds of Formula IV. The reduction processes are illustrated by the following equations.



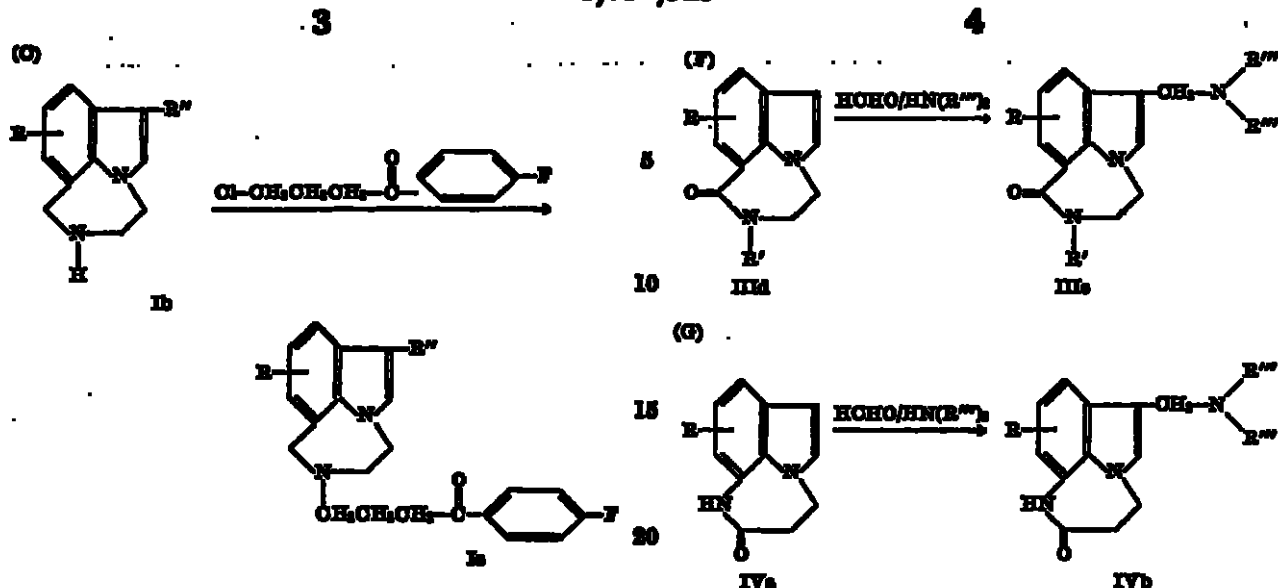
wherein R and R'' are the same as above, and R₁' is selected from the group consisting of hydrogen, alkyl of from 1 to 3 carbon atoms, inclusive, and



wherein R''' and n are the same as above.

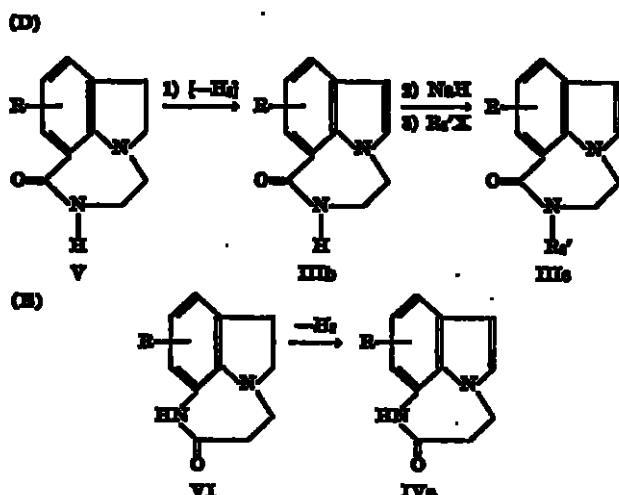
Compounds of Formula I wherein R' is 4-oxo-4-(p-fluorophenyl)butyl can be prepared by a process illustrated by Equation C.

8,784,919

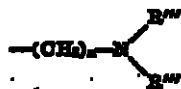


wherein R and R'' are the same as above.

Compounds of Formulas III and IV wherein R'' is hydrogen can be prepared by the processes illustrated by Equations D and E, respectively.

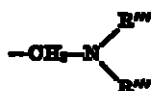


wherein R is the same as above, R' is selected from the group consisting of alkyl of from 1 to 3 carbon atoms, inclusive, 4-oxo-4-(p-fluorophenyl)butyl, and the group



wherein R''' is the same as above, and X is halogen, preferably chlorine or bromine.

Compounds of Formulas III and IV wherein R'' is



can be prepared by the processes illustrated by Equations F and G, respectively.

wherein R, R' and R''' are the same as above.

DETAILED DESCRIPTION

Processes A and B are conducted by reacting the 4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-ones (IIIa) and the 4,5-dihydropyrrolo[1,2,3-sf][1,5]benzodiazepin-6(7H)-ones (IV), respectively, with either lithium aluminum hydride or diborane in the presence of an aprotic solvent such as ether, dioxane, tetrahydrofuran or diglyme at a temperature of 0 to 100° C. and a reaction time of 1 to 18 hours. The product is recovered from the reaction mixture by conventional procedures, such as crystallization, evaporation, chromatography and combinations thereof.

This method is not utilized to prepare compounds of Formula I wherein R' is 4-oxo-4-(p-fluorophenyl)butyl because the carbonyl in the side chain as well as the carbonyl of the lactam moiety could be reduced thereby.

In process C, compounds of Formula I wherein R' is 4-oxo-4-(p-fluorophenyl)butyl are prepared by refluxing compounds having the formula of Ib with 4-chloro-4'-fluorobutyrophenone in an inert solvent for 18 to 48 hours. Solvents that may be utilized include benzene, toluene, xylene, 4-methyl-2-pentanone and the like. Preferably, the reaction is conducted in the presence of a catalyst such as potassium iodide and an acid acceptor such as sodium carbonate. The product is recovered by conventional procedures such as crystallization, evaporation, chromatography or a combination thereof.

In process D, the 4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-ones (IIIb) are prepared by dehydrogenating the corresponding 1,2,4,5-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-ones (V). This dehydrogenation may be performed by either of two procedures.

In the first procedure the dehydrogenation is conducted by reacting the appropriate 1,2,4,5-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one (V) with a palladium catalyst in the presence of an inert solvent at a temperature of from 100-200° C. for a period of 1 to 3 hours. Solvents that can be used in this procedure include quinoline, decalin, p-cymene, naphthalene and mesitylene. The product is recovered by conventional procedures such as crystallization, evaporation, chromatography and combinations thereof. This procedure cannot be utilized to prepare compounds of Formula IIIb wherein R is halogen because the procedure removes halogen substituents from the aromatic ring.

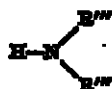
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In the second dehydrogenation procedure, the 1,2,4,5-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one is refluxed with either chloroanil or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in the presence of an inert solvent for 2 to 18 hours. Solvents that can be used in this procedure include benzene, toluene, xylene and the like. The product is recovered by conventional procedures such as crystallization, evaporation, chromatography and combinations thereof.

Compounds of Formula IIIc are prepared in accordance with steps 2 and 3 of process D. In step 2, compounds of Formula IIIb are reacted with an alkali metal hydride in the presence of an inert solvent at a temperature of 75-125° C. for 0.5 to 2 hours to prepare the alkali metal salt of IIIb. Solvents that can be utilized include benzene, tetrahydrofuran, dioxane, diglyme, dimethylformamide and dimethyl sulfoxide. In step 3, the reaction mixture containing said alkali metal salt is reacted with an alkyl halide, 4-chloro-4'-fluorobutylphenone, or tert. aminoalkyl halide having the formula R₃' wherein X is halogen and R₃' is the same as above to produce IIIc. The product is recovered by conventional procedures such as crystallization, evaporation, chromatography and the like.

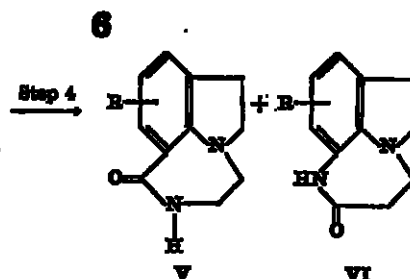
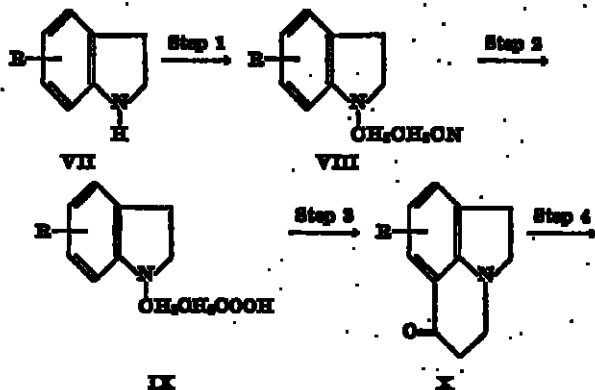
Process E, which is utilized to prepare 4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-ones (IVa) is conducted in the same manner and under the same conditions as step 1 of process D.

The 4,5 - dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-ones (IIIe) and the 4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-ones (IVb) are prepared by processes F and G, respectively. In process F the starting material is a compound of Formula IIIc, prepared in process D, and in process G the starting material is a compound of Formula IVa, prepared in process E. In these processes, the starting compounds are reacted with a mixture of 25% aqueous dialkylamine (having the formula



wherein R'' is the same as above), 37% aqueous formaldehyde and glacial acetic acid at a temperature of 25-50° C. for 1 to 18 hours. The product is recovered from the reaction mixture by conventional procedures such as crystallization, evaporation, chromatography and combinations thereof.

The 1,2,4,5 - tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-ones (V) and the 1,2,4,5-tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-ones (VI) employed as starting materials in the above processes D and E can be prepared by the process illustrated by the following equations in which R is the same as above.



Step 1 involves reacting the appropriate indoline (VII) with acrylonitrile to form a 1-indolinepropionitrile (VIII). In step 2, the 2-indolinepropionitrile is converted to the corresponding 1-indolinepropionic acid (IX). Step 3 involves heating the 1-indolinepropionic acid with polyphosphoric acid to form a 1,2,4,5-tetrahydro-6H-pyrrolo[3,2,1-jk]quinolin-6-one (X). The conditions utilized in these three steps are described in considerable detail in Rapoport et al., J. Org. Chem., 23, 248 (1958).

In step 4, the 1,2,4,5 - tetrahydro-6H-pyrrolo[3,2,1-jk]quinolin-6-one (X) is reacted with sodium azide in the presence of polyphosphoric acid to form a mixture of a 1,2,4,5 - tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one (V) and a 1,2,4,5 - tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one (VI). These compounds are readily separated by conventional procedures such as crystallization, evaporation, chromatography and combinations thereof. The preferred temperature at which this reaction is conducted is 50 to 60° C.; however, higher or lower temperatures may be utilized if desired. The molar ratio of ketone to sodium azide should be 1 to 1.3 and the reaction time is from 1 to 5 hours.

The acid addition salts of the invention comprise the salts of the compounds of Formulas I, II, III and IV as noted above, with pharmacologically acceptable acids such as sulfuric, hydrochloric, nitric, phosphoric, lactic, benzoic, methanesulfonic, p-toluenesulfonic, salicylic, acetic, propionic, maleic, malic, tartaric, citric, cyclohexanesulfamic, succinic, nicotinic, ascorbic acids, and the like.

The novel compounds of this invention exhibit tranquilizing and anticonvulsant activity. This activity was evaluated by use of the following tests.

CHIMNEY TEST [MED. EXP. 4, 11 (1961)]

This test determines the ability of mice to back up and out of a vertical glass cylinder within 30 seconds. Failure of mice to back up and out within this time indicates tranquilization.

DISH TEST

Mice in petri dishes (10 cm. diameter, 5 cm. high and partially imbedded in wood shavings) climb out in a very short time, when not treated. Mice remaining in the dish for more than 3 minutes indicates tranquilization.

PEDESTAL TEST

Mouse is placed on a pedestal. The untreated mouse leaves the pedestal in less than a minute to climb back to the floor of the standard mouse box. Tranquilized mice will stay more than 1 minute.

NICOTINE ANTAGONISM TEST

Thirty minutes after mice in a group are treated with the test compound, both the treated and untreated mice are injected with 2 mg./kg. of nicotine salicylate. The untreated mice show overstimulation, i.e., (1) running convulsion followed by (2) tonic extensor fits, followed by (3) death. An effective nicotine antagonist will protect the treated mice against (2) and (3).

The results of the above tests utilizing some of the novel compounds of this invention (administered intraperitoneally) are set forth in Table I. The results are expressed in terms of the mg./kg. dosages at which the tested compounds exhibited activity in 50% of the mice (ED₅₀). The structures of the various compounds are set forth in Table II.

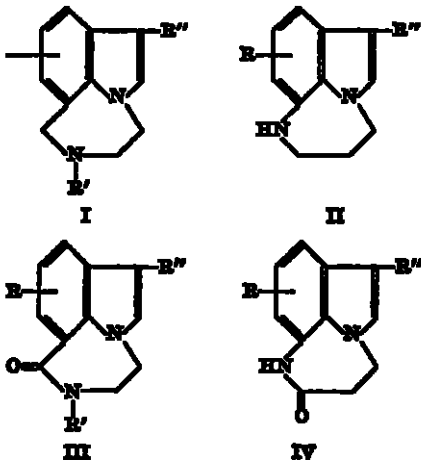
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TABLE I

Compound	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Test:																	
Obituary	45	10	>100	>100	>100	11	>100	40	25	>100	>100	>100	25	20	16	45	25
Dish	10	10	>100	>100	45	7.1	>100	25	25	>100	>100	>100	25	20	22	25	25
Feestal	5	25	>100	65	>100	14	>100	>100	25	25	>100	>100	25	25	22	25	25
N.A.:																	
TE	15	11	12	16	45	12.5	25	>100	15	25	>100	40	45	>100	15	200	65
D	25	11	12	25	45	12.5	25	>100	15	25	>100	40	45	>100	15	150	65

NOTE.—N.A.—Nicotine Antagonism; TE—Tonic Extensor Fit; D—Death.

TABLE II

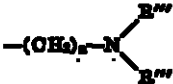


Compound	Formula	R	R'	R''
1	I	H	H	H
2	I	H-Cl	H	H
3	I	H	$-(CH_2)_2N(CH_2)_2$	H
4	I	H	$-(CH_2)_2N(CH_2)_2$	H
5	I	H	CH_3	H
6	I	H	$-(CH_2)_2O-C(=O)-C_6H_4-F$	H
7	I	H	H	$-(CH_2)_2N(CH_2)_2$
8	I	H	H	$-(CH_2)_2N(CH_2)_2$
9	I	H	H	H
10	I	H	H	H
11	I	H	H	H
12	I	H	$-(CH_2)_2N(CH_2)_2$	H
13	I	H	$-(CH_2)_2N(CH_2)_2$	H
14	I	H	CH_3	H
15	I	H	H	$-(CH_2)_2N(CH_2)_2$
16	I	H	H	$-(CH_2)_2N(CH_2)_2$
17	IV	H	H	$-(CH_2)_2N(CH_2)_2$

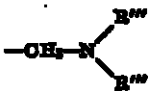
For purposes of administration to birds and to mammals, including animals of economic value such as horses, cattle, sheep, pigs, mice, rats, rabbits and the like, the novel compounds of the invention can be combined with solid or liquid pharmaceutical carriers and formulated in the form of tablets powder packets capsules and the like solid dosage forms, using starch and like excipients, or dissolved in suitable solvents or vehicles for oral or parenteral administration.

Also, for mammals and birds food premixes, with starch, oatmeal, dried fishmeal, fishmeal flour and the like can be prepared.

The novel compounds of this invention having the formulae (a) I and II and (b) III and IV wherein R' is



or R'' is



as defined above also form thiocyanic acid addition salts which when condensed with formaldehyde, form resinous materials useful as pickling inhibitors according to U.S. Pat. 2,425,320 and U.S. Pat. 2,606,155. The fluosilicic acid

addition salts of said compounds are useful as moth-proofing agents according to U.S. Pats. 1,915,334 and 2,075,359.

The following examples are set forth to illustrate my invention and to enable persons skilled in the art to better understand and practice the invention and are not intended to limit the same.

Example 1.—4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one

A mixture of 17.5 g. (0.0930 mole) of 1,2,4,5-tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one, 280 ml. of decalin and 8.4 g. of 10% palladium-on-carbon catalyst is refluxed under nitrogen for 1.5 hours, cooled and diluted with 1000 ml. of Skellysolve B hexanes. This mixture is kept in an ice bath for 2 hours and then filtered. The solid is washed with Skellysolve B hexanes and extracted with hot methanol. The methanol extract is concentrated, and the residue is crystallized from methanol-ethyl acetate to give 14.1 g. of crude product. This product is recrystallized from ethyl acetate to yield 4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one, melting point 210-214° C.

Analysis.—Calcd. for $C_{11}H_{10}N_2O$ (percent): C, 70.95; H, 5.41; N, 15.05. Found (percent): C, 71.06; H, 5.41; N, 14.71.

8,734,919

9

Example 2.—4,5,6,7-tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepine

A solution of 11.1 g. (0.0592 mole) of 4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one (Example 1) in 900 ml. of tetrahydrofuran is added under nitrogen to a stirred, refluxing suspension of 11 g. of lithium aluminum hydride in 500 ml. of tetrahydrofuran and the resulting mixture is refluxed for 18 hours, cooled in an ice bath and treated successively with 11 ml. of water, 11 ml. of 15% aqueous sodium hydroxide and 33 ml. of water. This mixture is stirred for about 1 hour and filtered. The filtrate is concentrated in vacuo and the residue is crystallized from ethyl acetate-Skellysolve B hexanes to give 7.87 g. of crude product. This product is recrystallized from ethyl acetate-Skellysolve B hexanes to yield 4,5,6,7-tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepine, melting point 79.5–80.5° C.

Analysis.—Calcd. for $C_{11}H_{13}N_2$ (percent): C, 76.71; H, 7.02; N, 16.27. Found (percent): C, 76.82; H, 7.13; N, 16.21.

Example 3.—9-chloro-4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one

A stirred mixture of 38.9 g. (0.175 mole) of 9-chloro-1,2,4,5-tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepine-6(7H)-one, 48 g. (0.211 mole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and 780 ml. of benzene is refluxed under nitrogen for 7 hours and allowed to stand at ambient temperature for 18 hours. The solid is collected by filtration, washed with benzene, and stirred for 1.5 hours with a mixture of dilute aqueous sodium hydroxide (1.5 l.) and methylene chloride (1.5 l.). The resulting solid is collected by filtration and washed with dilute aqueous sodium hydroxide. The aqueous filtrate is extracted with methylene chloride, and the solid is extracted several times with boiling methylene chloride. The combined methylene chloride extracts are washed with a saturated solution of sodium chloride, dried over anhydrous potassium carbonates and concentrated in vacuo. The residue is crystallized from methylene chloride-methanol (decolorizing charcoal treatment) to give 20.5 g. of crude product. The product is recrystallized from methylene chloride-methanol to give 9-chloro-4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one, melting point 234–235° C.

Analysis.—Calcd. for $C_{11}H_9ClN_2O$ (percent): C, 59.87; H, 4.11; Cl, 16.87; N, 12.70. Found (percent): C, 59.85; H, 4.26; Cl, 16.24; N, 12.86.

Example 4.—9-chloro-4,5,6,7-tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepine

A solution of 8.0 g. (0.0364 mole) of 9-chloro-4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one (Example 3) in 600 ml. of tetrahydrofuran is added under nitrogen to a stirred, refluxing suspension of 8.0 g. of lithium aluminum hydride in 400 ml. of tetrahydrofuran, and the resulting mixture is refluxed for 8 hours and allowed to stand at ambient temperature for 18 hours. This mixture is cooled in an ice bath and treated successively with 8 ml. of water, 8 ml. of 15% aqueous sodium hydroxide and 24 ml. of water. The resulting mixture is stirred for 1 hour and filtered. The filtrate is concentrated in vacuo, and the residue is crystallized from ethyl acetate-Skellysolve B hexanes to give 6.3 g. of crude product. The product is recrystallized from ethyl acetate-Skellysolve B hexanes to give 9-chloro-4,5,6,7-tetrahydropyrrolo[1,2,3-ef][1,5]benzodiazepine, melting point 128.5–129.5° C.

Analysis.—Calcd. for $C_{11}H_{11}ClN_2$ (percent): C, 63.92; H, 5.37; Cl, 17.16; N, 13.56. Found (percent): C, 64.20; H, 5.37; Cl, 17.17; N, 13.55.

Example 5.—1-(dimethylaminomethyl)-4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one

A solution of 25% aqueous dimethylamine (2.43 ml.) is cooled with stirring in an ice bath and treated succe-

10

sively with 5.0 ml. of acetic acid and 0.893 ml. of 37% aqueous formaldehyde. This solution is allowed to warm to ambient temperature and is treated with 1.86 g. (0.010 mole) of 4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one (Example 1). This mixture is stirred, under nitrogen, for 3 hours and poured into ice water. The cold solution is made alkaline with sodium hydroxide and the precipitate is collected by filtration, washed with water and dried to give 2.17 g. of crude product. Recrystallization of this product twice from methanol-ethyl acetate yields 1-(dimethylaminomethyl)-4,5-dihydropyrrolo[1,2,3-ef][1,5]benzodiazepin-6(7H)-one, melting point 193–193.5° C.

Analysis.—Calcd. for $C_{14}H_{19}N_3O$ (percent): C, 69.11; H, 7.04; N, 17.27. Found (percent): C, 68.90; H, 6.92; N, 17.06.

Example 6.—4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one

A stirred mixture of 23.8 g. (0.127 mole) of 1,2,4,5-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one, 380 ml. of decalin and 11.5 g. of 10% palladium-on-carbon catalyst is refluxed under nitrogen for 1.5 hours. The mixture is cooled in an ice bath, diluted with 450 ml. of Skellysolve B hexanes and allowed to crystallize. The solid is collected by filtration, washed with Skellysolve B hexanes and extracted with methanol. The methanol extract is concentrated under reduced pressure, and the residue is crystallized from ethanol-ethyl acetate to give 16.19 g. of crude product. This crude product is recrystallized from methanol-ethyl acetate to yield 4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one, melting point 173–174° C.

Analysis.—Calcd. for $C_{11}H_{13}N_2O$ (percent): C, 70.95; H, 5.41; N, 15.05. Found (percent): C, 71.34; H, 5.41; N, 15.01.

Example 7.—4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepine

A solution of 11.2 g. (0.0604 mole) of 4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one (Example 6) in 900 ml. of dry tetrahydrofuran is added under nitrogen to a stirred, refluxing suspension of 11.5 g. of lithium aluminum hydride in 500 ml. of tetrahydrofuran. The resulting mixture is refluxed for 18 hours, cooled in an ice bath and treated successively with 11.5 ml. of water, 11.5 ml. of 15% aqueous sodium hydroxide and 34.5 ml. of water. The solid is collected by filtration and the filtrate is concentrated under reduced pressure. Crystallization of the residue from ethyl acetate-Skellysolve B hexanes gives 5.32 g. of crude product. Recrystallization of this crude product from ethyl acetate-Skellysolve B hexanes yields 4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepine, melting point 62.5–63.5° C.

Analysis.—Calcd. for $C_{11}H_{13}N_2$ (percent): C, 76.71; H, 7.02; N, 16.27. Found (percent): C, 76.83; H, 7.05; N, 16.12.

Example 8.—9-chloro-4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one

A stirred mixture of 10.0 g. (0.0450 mole) of 9-chloro-1,2,4,5-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one, 12.3 g. (0.0542 mole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and 200 ml. of dry benzene is refluxed under nitrogen for 7 hours, cooled and filtered. The resulting solid is suspended in a mixture of about 400 ml. of cold dilute aqueous sodium hydroxide and about 400 ml. of methylene chloride, stirred for 30 minutes and mixture is filtered. The methylene chloride solution is washed with a saturated solution of sodium chloride, dried over anhydrous potassium carbonate and concentrated. Crystallization of the residue from tetrahydrofuran (decolorizing charcoal treatment) gives 2.20 g. of crude product. The sticky solid obtained from the above filtration is mixed with diatomaceous earth, washed several times with cold,

8,734,919

13

6 - [3-(dimethylamino)propyl]-4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepine dihydrochloride.

Example 14.—4,5-dihydro-6-methylpyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one

A stirred solution of 10.0 g. (0.0538 mole) of 4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one (Example 6) in 300 ml. of dry dimethylformamide is cooled in an ice bath under nitrogen and treated with a 57.1% mineral oil suspension of sodium hydride (2.43 g.). The resulting mixture is warmed on the steam bath for 1 hour, cooled in an ice bath and treated with a solution of 8.38 g. of methyl iodide in 90 ml. of ether. This mixture is kept at ambient temperature for 18 hours and concentrated in vacuo. The residue is suspended in water and extracted with methylene chloride. The extract is dried over anhydrous potassium carbonate and concentrated in vacuo. The residue is chromatographed on 800 g. of silica gel with 50% acetone-50% Skellysolve B hexanes (by volume). The desired crude product is the first material eluted from the column. This product is recrystallized twice from ethyl acetate-Skellysolve B hexanes to yield 4,5-dihydro-6-methylpyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one, melting point 105.5–106.5° C.

Analysis.—Calcd. for $C_{12}H_{13}N_2O$ (percent): C, 71.98; H, 6.04; N, 13.99. Found (percent): C, 71.98; H, 5.70; N, 13.96.

Example 15.—4,5,6,7-tetrahydro-6-methylpyrrolo[3,2,1-jk][1,4]benzodiazepine

A solution of 5.32 g. (0.0266 mole) of 4,5-dihydro-6-methylpyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one (Example 14) in 150 ml. of tetrahydrofuran is added, under nitrogen, to a stirred, refluxing suspension of 5.3 g. of lithium aluminum hydride in 200 ml. of tetrahydrofuran. The resulting mixture is refluxed for 18 hours, cooled in an ice bath and treated successively with 5.3 ml. of water, 5.3 ml. of 15% aqueous sodium hydroxide and 15.9 ml. of water. This mixture is stirred for about 1 hour and filtered. The filtrate is concentrated in vacuo. Recrystallization of the residue twice from petroleum ether, at 0° C., gives 4,5,6,7-tetrahydro-6-methylpyrrolo[3,2,1-jk][1,4]benzodiazepine, melting point 42.5–44° C.

Analysis.—Calcd. for $C_{12}H_{15}N_2$ (percent): C, 77.38; H, 7.58; N, 15.04. Found (percent): C, 77.06; H, 7.44; N, 14.82.

Example 16.—4'-fluoro-4-(4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-6(7H)yl)butyrophenone

A mixture of 1.72 g. (0.010 mole) of 4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepine (Example 7), 2.82 g. of 4-chloro-4'-fluorobutyrophenone, 3.22 g. of anhydrous sodium carbonate, 70 mg. of potassium iodide and 130 ml. of 4-methyl-2-pentanone is refluxed under nitrogen for 14 hours, cooled and poured into ice water. The layers are separated and the aqueous layer is extracted with ether. The combined organic layer is dried over anhydrous potassium carbonate and concentrated in vacuo. The residue is chromatographed on 200 g. of silica gel with 70% ethyl acetate-30% cyclohexane (by volume) and 100 ml. fractions are collected. The crude product is eluted in fractions 14–23 and recrystallized twice from ethyl acetate-Skellysolve B hexanes to give 4'-fluoro-4-(4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-6(7H)yl)butyrophenone, melting point 90–91° C.

Analysis.—Calcd. for $C_{22}H_{21}FN_2O$ (percent): C, 74.97; H, 6.29; F, 5.65; N, 8.33. Found (percent): C, 74.80; H, 6.27; F, 5.59; N, 8.50.

Example 17.—1-(dimethylaminomethyl)-4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one

A solution (2.43 ml.) of 25% aqueous dimethylamine is cooled with stirring in an ice bath and treated successively with 5 ml. of acetic acid and 0.893 ml. of 37% aqueous formaldehyde. This solution is allowed to warm

14

to ambient temperature and is treated with 1.86 g. (0.010 mole) of 4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one (Example 6). This mixture is stirred, under nitrogen, for 2 hours and poured into ice water. The resulting solution is made alkaline with dilute aqueous sodium hydroxide and extracted with methylene chloride. The extract is dried over anhydrous potassium carbonate and concentrated in vacuo. The residue is treated with ethyl acetate and a small amount of insoluble material is removed by filtration. The filtrate is concentrated and crystallized to yield 1.43 g. of crude product. This product is recrystallized from ethyl acetate to give 1-(dimethylaminomethyl)-4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one, melting point 171–172.5° C.

Analysis.—Calcd. for $C_{14}H_{17}N_3O$ (percent): C, 69.11; H, 7.04; N, 17.27. Found (percent): C, 69.22; H, 7.24; N, 17.30.

Example 18.—1-(dimethylaminomethyl)-4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepine and dihydrobromide thereof

1-(dimethylaminomethyl)-4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one (9.64 g., 0.0392 mole) (Example 17) is added, under nitrogen, to an ice cold stirred suspension of 9.6 g. of lithium aluminum hydride in 1.2 l. of tetrahydrofuran, and the resulting mixture is refluxed for 7 hours and kept at ambient temperature for 18 hours. It is then cooled in an ice bath and treated successively with 9.6 ml. of water, 9.6 ml. of 15% aqueous sodium hydroxide and 28.8 ml. of water. The solid is collected by filtration, and the filtrate is concentrated in vacuo. The residue is crystallized at 6° C. from ethyl acetate-Skellysolve B hexanes to give 7.38 g. of crude product. Recrystallization of this product from ethyl acetate-Skellysolve B hexanes yields 1-(dimethylaminomethyl)-4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepine, melting point 67.5–68.5° C.

Analysis.—Calcd. for $C_{14}H_{19}N_3$ (percent): C, 73.32; H, 8.35; N, 18.33. Found (percent): C, 73.40; H, 8.32; N, 18.22.

A solution of 1-(dimethylaminomethyl)-4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepine in ethyl acetate is acidified with methanolic hydrogen bromide, and the resulting product is recrystallized from methanol-ethyl acetate to yield 1-(dimethylaminomethyl)-4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepine dihydrobromide, melting point 227° C. (dec.).

Analysis.—Calcd. for $C_{14}H_{19}N_3 \cdot 2HBr$ (percent): C, 42.98; H, 5.41; Br, 40.86; N, 10.74. Found (percent): C, 42.89; H, 5.28; Br, 40.70; N, 10.58.

Example 19.—9-chloro-1-(dimethylaminomethyl)-4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one

Aqueous dimethylamine (25%) (2.43 ml.) is cooled in an ice bath and treated successively with glacial acetic acid (5 ml.) and 27% aqueous formaldehyde (0.89 ml.). This solution is warmed to 18° C. and treated with 2.20 g. (0.010 mole) of 9-chloro-4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one (Example 8). This mixture is stirred at ambient temperature for 2 hours, at 40–50° C. for 1.25 hours and at 80° C. for 45 minutes. It is then poured into ice water and made alkaline with 15% aqueous sodium hydroxide. The initially formed gum crystallizes and is collected by filtration and dried to give 2.36 g. of 9-chloro-1-(dimethylaminomethyl)-4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one, melting point 228–231° C. (dec.).

Example 20.—9-chloro-1-(dimethylaminomethyl)-4,5,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepine and dihydrochloride thereof

To a stirred suspension of 2 g. of lithium aluminum hydride in 500 ml. of tetrahydrofuran is added 2.08 g. of 9-chloro-1-(dimethylaminomethyl)-4,5-dihydropyrrolo[3,2,1-jk][1,4]benzodiazepin-7(6H)-one (Example 19),

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