

OLARTE RAISBECK


Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO

Radicación : 00031252 00000004

Folios: 31

Fecha (AMD): 2005-01-07 15:49:05

Trámite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

SOLICITUD DE:

1

☐

Corrección de Error Material.

☒

Modificación a una Solicitud.

2

SOLICITANTE
(71)

Nombre: SCHERING CORPORATION.
Dirección: 2000 Galloping Hill Road,
Kenilworth, NJ 07033-0530, E.U.A.
Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: Kenilworth

Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A
Calle 100 No. 8ª-37 Piso 10. Bogotá
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: _____

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747Bta
TP 74.295

4

Número de expediente: 00.031.252

5

Descripción de la corrección o modificación solicitada VER PAGINA ADJUNTA.

6

Comprobante de pago No. 98, 594; 977

Fecha 12-22-04; 06-01-05

7

Anexos

☒

Comprobante de pago de la tasa.

☐

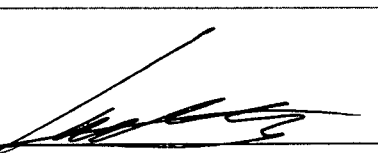
Poderes, si fuere el caso.

☐

Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

8

NOMBRE: CARLOS R. OLARTE

FIRMA: 

C.C. 79.782.747 Bta T.P. 74.295

Me permito ADICIONAR 2 nuevas reivindicaciones (Reivindicaciones 26 y 27) que pretenden reclamar el concepto inventivo de forma más específica. Aclaro que las reivindicaciones añadidas no comprenden una ampliación del concepto inventivo originalmente presentado y se encuentran en su totalidad sustentadas dentro del Capítulo Descriptivo de la presente solicitud.

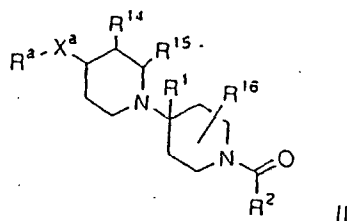
Reivindicación 26	Sustentada en el primer párrafo de la página 107 del Capítulo Descriptivo.
Reivindicación 27	Sustentada por la estructura molecular descrita en la página 57 del Capítulo Descriptivo, y específicamente por los radicales descritos en el ejemplo 5K de la pagina 58.

287
P
799

7296
705

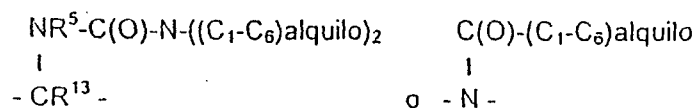
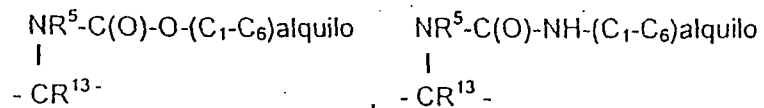
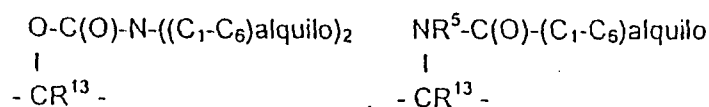
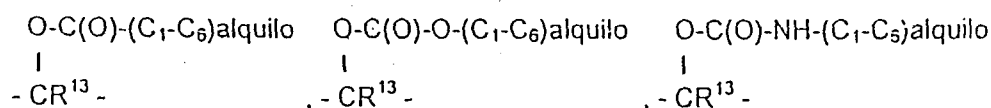
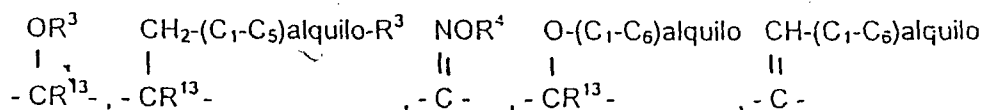
CAPITULO REIVINDICATORIO MODIFICADO

1. Un compuesto representado por la fórmula estructural II



o una sal farmacéuticamente aceptable del mismo, donde

(1) X^a es $-C(R^{13})_2$, $-C(R^{13})(R^{19})$, $-C(O)-$, $-O-$, $-NH-$, $-N((C_1-C_6)\text{alquilo})$,



2289
796

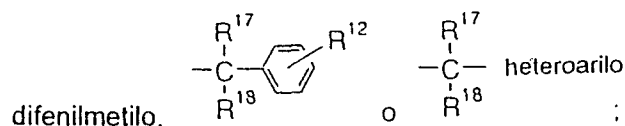
R^a es R^{6a} -fenilo, R^{6a} -piridilo, R^{6a} -tiofenilo o R^6 -naftilo;

R^1 es hidrógeno, alquilo C_1-C_6 o alquenilo C_2-C_6 ;

R^2 es R^7 , R^8 , R^9 -fenilo; R^7 , R^8 , R^9 -heteroarilo sustituido de 6 miembros;

R^7 , R^8 , R^9 -N-óxido de heteroarilo de 6 miembros sustituido;

R^{10} , R^{11} -heteroarilo sustituido de 5 miembros; naftilo; fluorenilo;

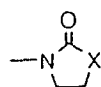


R^3 es R^{10} -fenilo, piridilo, pirimidilo, pirazinilo o tiazolilo;

R^4 es hidrógeno, alquilo C_1-C_6 ; fluor- C_1-C_6 alquilo, ciclopropilmetilo, $-CH_2CH_2OH$, $-CH_2CH_2O-(C_1-C_6)$ alquilo, $-CH_2C(O)-O-(C_1-C_6)$ alquilo, $-CH_2C(O)-NH_2$, $-CH_2C(O)-NH(C_1-C_6)$ alquilo o $-CH_2C(O)-N((C_1-C_6)alquilo)_2$;

R^5 y R^{11} están independientemente seleccionados del grupo que consiste en hidrógeno y (C_1-C_6) -alquilo;

R^{6a} representa de 1 a 3 sustituyentes independientemente seleccionados del grupo que consiste en hidrógeno, halógeno, $-CF_3$, CF_3O- , $-CN$, $-CF_3SO_2-$, R^{12} -

fenilo, $-NHCOCF_3$, heteroarilo de 5 miembros y , donde X es $-O-$, $-NH-$ o $-N(CH_3)-$;

R^6 está independientemente seleccionado del grupo que consiste en R^{6a} y CH_3SO_2- ;

R^7 y R^8 están independientemente seleccionados del grupo que consiste en (C_1-C_6) alquilo, halógeno, $-NR^{20}R^{21}$, $-OH$, $-CF_3$, $-OCH_3$, $-O$ -acilo, y $-OCF_3$;

R^9 es R^7 , hidrógeno, fenilo, $-NO_2$, $-CN$, $-CH_2F$, $-CHF_2$, $-CHO$, $-CH=NOR^{20}$, piridilo, N-óxido piridilo, pirimidinilo, pirazinilo, $-N(R^{20})CONR^{21}R^{22}$, $-NHCONH$ (cloro- (C_1-C_6) alquilo), $-NHCONH((C_3-C_{10})$ cicloalquilo (C_1-C_6) alquilo), $-NHCO(C_1-C_6)$ alquilo, $-NHCOCF_3$, $-NHSO_2N((C_1-C_6)alquilo)_2$, $-NHSO_2(C_1-C_6)-$

297
290

alquilo, $-\text{N}(\text{SO}_2\text{CF}_3)_2$, $-\text{NHCO}_2(\text{C}_1\text{-C}_6)\text{alquilo}$, $\text{C}_3\text{-C}_{10}$ cicloalquilo, $-\text{SR}^{23}$, $-\text{SOR}^{23}$, $-\text{SO}_2\text{R}^{23}$, $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_6\text{ alquilo})$, $-\text{OSO}_2(\text{C}_1\text{-C}_6)\text{alquilo}$, $-\text{OSO}_2\text{CF}_3$, hidroxil $(\text{C}_1\text{-C}_6)\text{-alquilo}$, $-\text{CON R}^{20}\text{R}^{21}$, $-\text{CON}(\text{CH}_2\text{CH}_2\text{-O-CH}_3)_2$, $-\text{OCONH}(\text{C}_1\text{-C}_6)\text{alquilo}$, $-\text{CO}_2\text{R}^{20}$, $-\text{Si}(\text{CH}_3)_3$ o $-\text{B}(\text{OC}(\text{CH}_3)_2)_2$;

R^{10} es $(\text{C}_1\text{-C}_6)\text{alquilo}$, $-\text{NH}_2$ o $\text{R}^{12}\text{-fenilo}$;

R^{12} representa de 1 a 3 substituyentes independientemente seleccionados del grupo que consiste en hidrógeno, $(\text{C}_1\text{-C}_6)\text{alquilo}$, $-\text{CF}_3$, $-\text{CO}_2\text{R}^{20}$, $-\text{CN}$, $(\text{C}_1\text{-C}_6)\text{alcoxi}$ y halógeno;

R^{13} , R^{14} , R^{15} y R^{16} están independientemente seleccionados del grupo que consiste en hidrógeno y $(\text{C}_1\text{-C}_6)\text{alquilo}$;

R^{17} y R^{18} están independientemente seleccionados del grupo que consiste en hidrógeno y alquilo $\text{C}_1\text{-C}_6$, o R^{17} y R^{18} conjuntamente son un grupo alquilenil $\text{C}_2\text{-C}_5$ y con el carbono al cual están unidos forman un anillo espiro de 3 a 6 átomos de carbono;

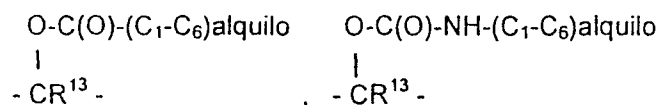
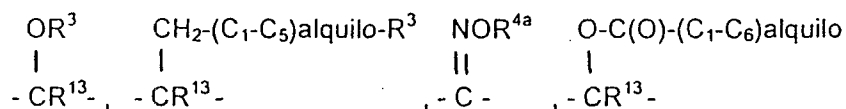
R^{19} es $\text{R}^6\text{-fenilo}$, $\text{R}^6\text{-heteroarilo}$, $\text{R}^6\text{-naftilo}$, cicloalquilo $\text{C}_3\text{-C}_{10}$, $(\text{C}_3\text{-C}_{10})\text{cicloalquil}(\text{C}_1\text{-C}_6)\text{alquilo}$ o $(\text{C}_1\text{-C}_6)\text{alcoxi}(\text{C}_1\text{-C}_6)\text{alquilo}$;

R^{20} , R^{21} y R^{22} están independientemente seleccionados del grupo que consiste en H y alquilo $\text{C}_1\text{-C}_6$; y

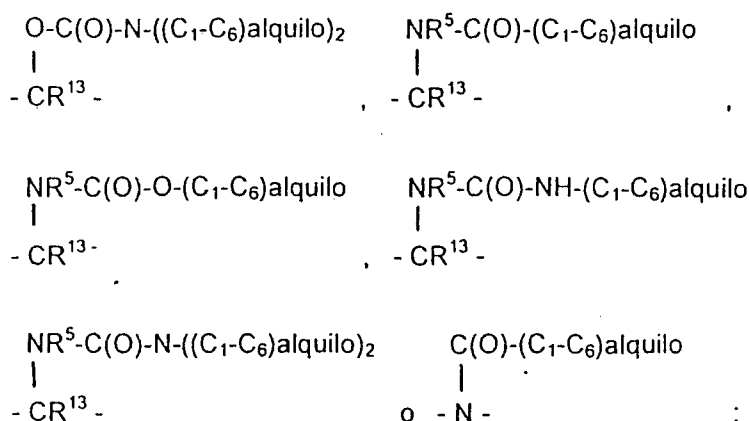
R^{23} es alquilo $\text{C}_1\text{-C}_6$ o fenilo; o

(2):

X^a es $-\text{C}(\text{R}^{13})(\text{R}^{19})-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{NH}-$, $-\text{N}((\text{C}_1\text{-C}_6)\text{alquilo})-$,



7af
291

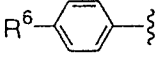


R^a es R^{6b} -fenilo, R^{6b} -piridilo o R^{6b} -tiofenilo;

R^{4a} es flúor- C_1-C_6 alquilo, ciclopropilmetilo, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2-\text{O}-(\text{C}_1-\text{C}_6)\text{alquilo}$, $-\text{CH}_2\text{C}(\text{O})-\text{O}-(\text{C}_1-\text{C}_6)\text{alquilo}$, $-\text{CH}_2\text{C}(\text{O})-\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})-\text{NH}(\text{C}_1-\text{C}_6)\text{alquilo}$ o $-\text{CH}_2\text{C}(\text{O})-\text{N}((\text{C}_1-\text{C}_6)\text{alquilo})_2$;

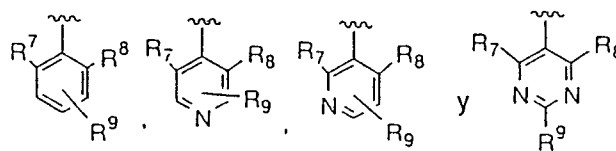
R^{6b} es CH_3SO_2- ; y

$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^5, \text{R}^{14}, \text{R}^{15}, \text{R}^{16}$ y R^{19} son como se han definido en (1).

2. El compuesto de la reivindicación 1 en el cual R^a es 
3. El compuesto de la reivindicación 1, fórmula II(1), en el cual X^a es $-\text{CHOR}^3$, $-\text{C}(\text{R}^{13})(\text{R}^{19})-$ o $-\text{C}(=\text{NOR}^{4a})$.
4. El compuesto de la reivindicación 3, en el cual R^3 es piridilo, R^4 es alquilo (C_1-C_6), o R^{13} es hidrógeno y R^{19} es R^6 -fenilo.
5. El compuesto de la reivindicación 1, fórmula II(2), en el cual X^a es $-\text{CHOR}^3$, $-\text{C}(\text{R}^{13})(\text{R}^{19})-$ o $-\text{C}(=\text{NOR}^{4a})$.
6. El compuesto de la reivindicación 5, en el cual R^3 es piridilo, R^{4a} es ciclopropilmetilo o trifluoretilo, o R^{13} es hidrógeno y R^{19} es R^6 -fenilo.
7. El compuesto de la reivindicación 1, en el cual R^2 es $\text{R}^7, \text{R}^8, \text{R}^9$ -fenilo; $\text{R}^7, \text{R}^8, \text{R}^9$ -piridilo o un N-óxido del mismo; o $\text{R}^7, \text{R}^8, \text{R}^9$ -pirimidilo.

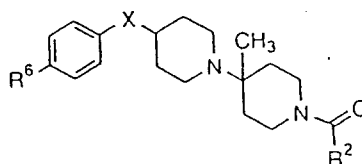
799
292

8. El compuesto de la reivindicación 7, en el cual R^2 está seleccionado del grupo que consiste en



donde R^7 y R^8 están seleccionados del grupo que consiste en (C_1-C_6) alquilo, halógeno, y $-NH_2$, y R^9 es hidrógeno.

9. Un compuesto de la reivindicación 1 seleccionado del grupo que consiste en los que están representados por la fórmula



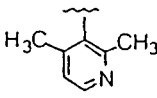
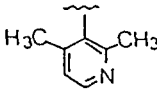
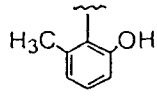
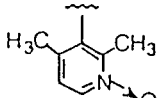
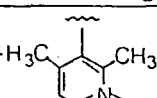
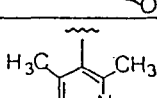
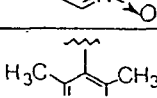
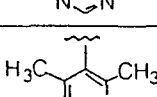
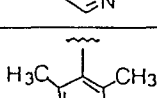
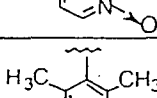
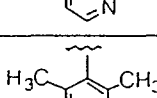
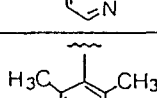
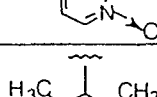
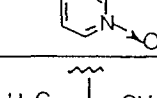
en la cual R^6 , X y R^2 son tal como se definen en la tabla siguiente:

R^6	X	R^2
Br	$\begin{array}{c} OCH_2CH_3 \\ \\ -CH- \end{array}$	
Br	$\begin{array}{c} OCOCH_2CH_3 \\ \\ -CH- \end{array}$	
Br	$\begin{array}{c} OCOOCH_3 \\ \\ -CH- \end{array}$	
Br	$\begin{array}{c} OCONHCH_3 \\ \\ -CH- \end{array}$	
Br		
Br	$\begin{array}{c} OCOOCH_2CH_3 \\ \\ -CH- \end{array}$	
Br	$\begin{array}{c} OCOCH_3 \\ \\ -CH- \end{array}$	
Br	$\begin{array}{c} OCO(CH_2)_2CH_3 \\ \\ -CH- \end{array}$	
Br	$\begin{array}{c} OCONHCH_2CH_3 \\ \\ -CH- \end{array}$	

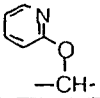
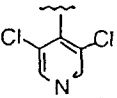
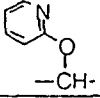
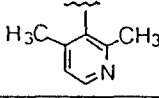
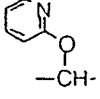
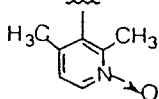
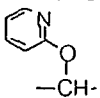
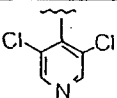
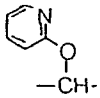
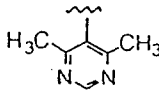
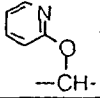
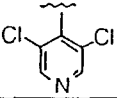
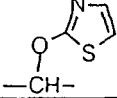
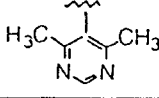
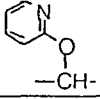
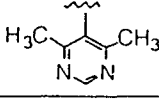
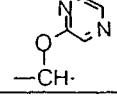
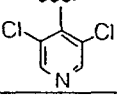
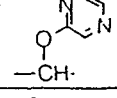
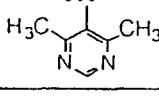
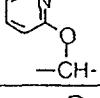
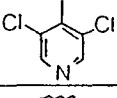
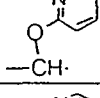
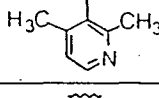
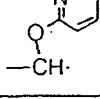
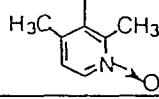
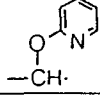
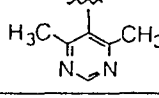
203

Br		
Br		
Br		
CH3SO2-		
Br		
Br		
Br		
Br		
H3CSO2-		
H3CSO2-		
F3C-		
H3CSO2-		
H3CSO2-		
F3CO-		
F3CO-		

294

F ₃ CO-		
Br		
Br		
F ₃ CO-		
Br		
Br		
H ₃ CSO ₂ -		
H ₃ CSO ₂ -		
H ₃ CSO ₂ -		
H ₃ CSO ₂ -		
H ₃ CSO ₂ -		
H ₃ CSO ₂ -		
F ₃ C-		
F ₃ CO-		

295
100 302

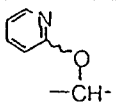
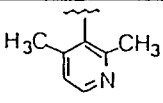
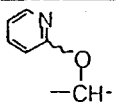
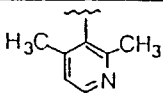
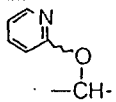
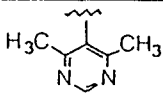
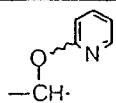
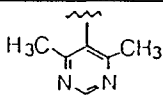
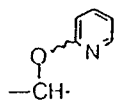
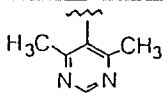
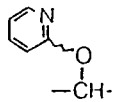
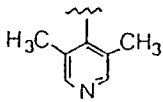
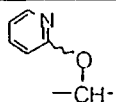
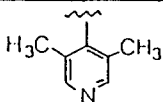
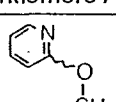
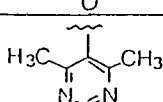
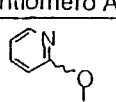
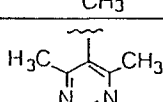
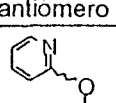
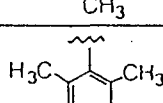
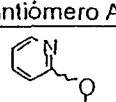
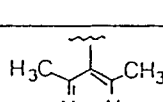
F_3CO-		
Cl		
Cl		
Cl		
Cl		
Br		
H_3CSO_2-		
F_3C-		
H_3CSO_2-		
H_3CSO_2-		
F_3C-		
F		
F		
F		

29/6
XX 303

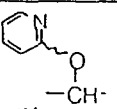
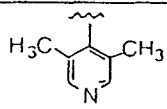
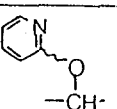
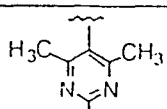
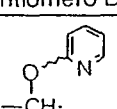
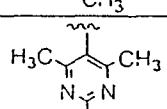
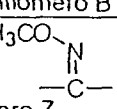
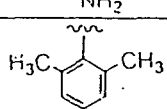
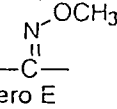
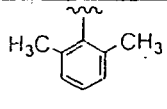
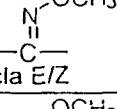
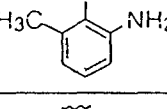
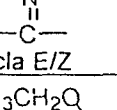
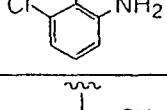
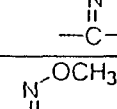
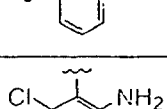
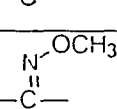
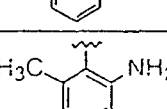
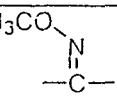
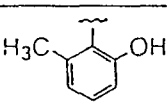
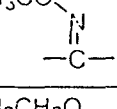
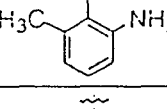
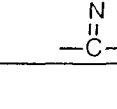
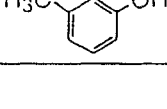
Cl		
F		
Br		
Br		
Br		
Br		
F3C-		
F3C-		
F3C-		
F		
Br		
Br		

Enantiómero A

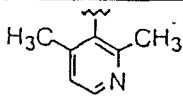
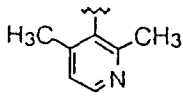
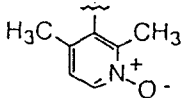
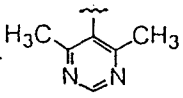
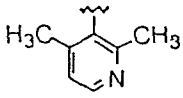
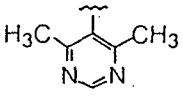
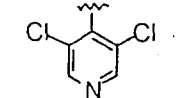
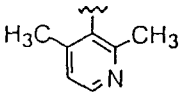
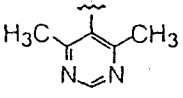
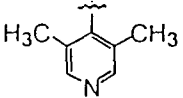
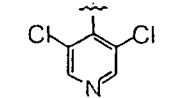
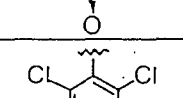
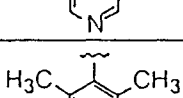
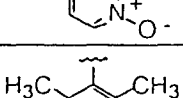
19297
fold

Br	 Enantiómero A	
Br	 Enantiómero B	
Br	 Enantiómero B	
F ₃ CO-	 Enantiómero A	
F ₃ CO-	 Enantiómero B	
F ₃ CO-	 Enantiómero A	
F ₃ CO-	 Enantiómero A	
F ₃ CO-	 Enantiómero A	
F ₃ CO-	 Enantiómero B	
Cl	 Enantiómero A	
Cl	 Enantiómero A	

23/10/2006

Cl	 Enantiómero B	
Cl	 Enantiómero B	
F ₃ CO-	 Enantiómero B	
Br	 Isómero Z	
Br	 Isómero E	
Br	 Mezcla E/Z	
Br	 Mezcla E/Z	
Br	 Mezcla E/Z	
Br	 Mezcla E/Z	
Br	 Mezcla E/Z	
Br	 Mezcla E/Z	
Br	 Mezcla E/Z	

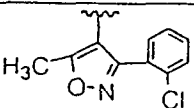
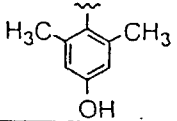
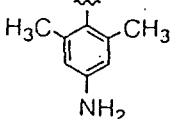
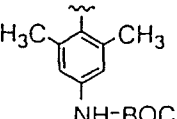
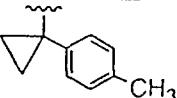
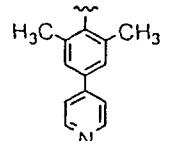
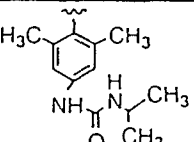
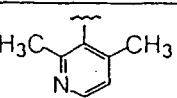
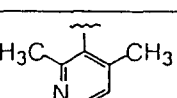
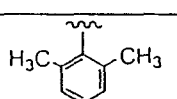
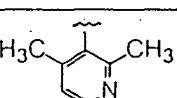
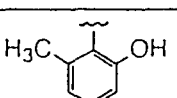
34
299

Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{CO}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{CO}-\text{N}=\text{C}-$	
Br	$\text{OCH}_2\text{CH}_3-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CF}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CF}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{CO}-\text{N}=\text{C}-$	
Br	$\text{CH}_3(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	

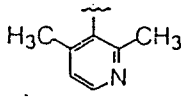
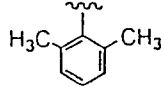
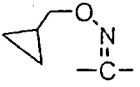
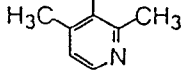
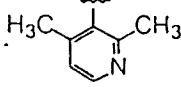
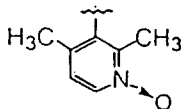
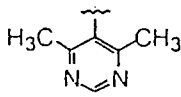
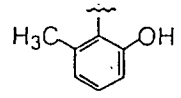
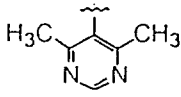
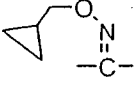
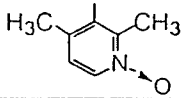
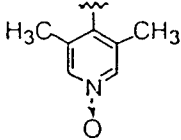
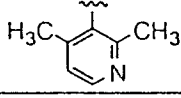
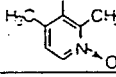
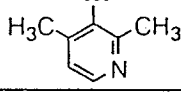
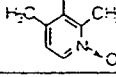
300

Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
Br	$\text{H}_3\text{C}-\text{CH}(\text{H}_3\text{C})-\text{O}-\text{N}=\text{N}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
Br		
Br	$\text{H}_3\text{C}-\text{CH}(\text{H}_3\text{C})-\text{O}-\text{N}=\text{N}-\text{C}-$	
Br	$\text{H}_3\text{CO}-\text{N}=\text{N}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
F3C-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	

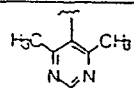
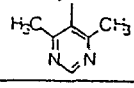
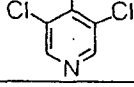
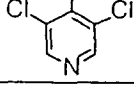
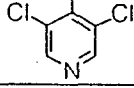
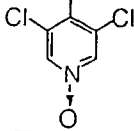
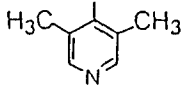
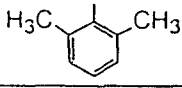
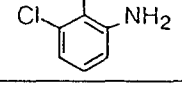
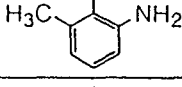
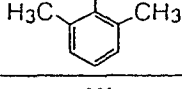
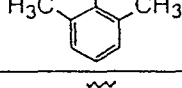
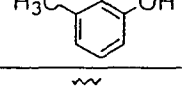
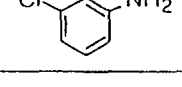
16-304
301

Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
F ₃ CO-	$\text{H}_3\text{CO}-\text{N}=\text{C}-$ Isómero Z	
F ₃ CO-	$\text{H}_3\text{CO}-\text{N}=\text{C}-$ Isómero E	
Br	$\text{H}_3\text{C}-\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{C}-\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{C}-\text{O}-\text{N}=\text{C}-$	

173
302

Br	$\text{H}_3\text{CO}(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{CO}(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	
Br		
$\text{F}_3\text{CO}-$	$\text{F}_3\text{CCH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{F}_3\text{CCH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{F}_3\text{CCH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{F}_3\text{CCH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$		
Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Cl	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	

1834
303

Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ C-	$\text{CH}_3\text{O}-\text{N}=\text{N}-\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ C-	$\text{CH}_3\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ C-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ CO-	$\text{CH}_3\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ CO-	$\text{CH}_3\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ CO-	$\text{CH}_3\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ CO-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ C-	$\text{CH}_3\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ CO-	$\text{CH}_3\text{O}-\text{N}=\text{N}-\text{C}-$	
F ₃ C-	$\text{CH}_3\text{O}-\text{N}=\text{N}-\text{C}-$ Isómero E	

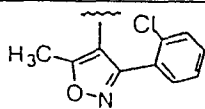
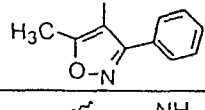
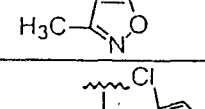
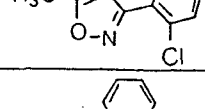
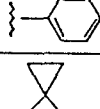
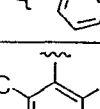
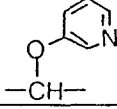
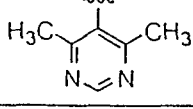
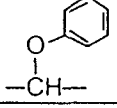
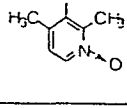
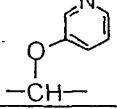
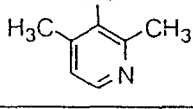
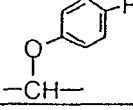
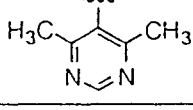
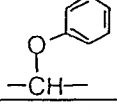
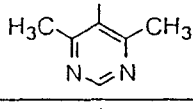
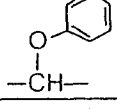
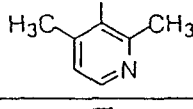
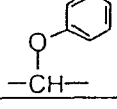
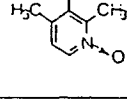
1234
304

F ₃ C-	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
F ₃ C-	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
F ₃ CO-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
F ₃ C-	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
F ₃ C-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
F ₃ CO-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
F ₃ CO-		
F ₃ CO-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
F ₃ C-	$\text{CH}_3\text{O}-\text{N}=\text{C}-$ Isómero E	
F ₃ CO-	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
F ₃ CO-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
F ₃ C-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
F ₃ C-	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
F ₃ CO-	$\text{CH}_3\text{O}-\text{N}=\text{C}-$ Isómero E	
F ₃ CO-	$\text{H}_3\text{CO}(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	

2034
305

F ₃ CO-	CH ₃ CH ₂ O- N=N- -C-	
F ₃ CO-	 N=N- -C-	
F ₃ CO-	 N=N- -C-	
F ₃ CO-	CH ₃ CH ₂ O- N=N- -C-	
F ₃ CO-	CH ₃ O- N=N- -C-	
F ₃ CO-	CH ₃ CH ₂ O- N=N- -C-	
F ₃ CO-	CH ₃ CH ₂ O- N=N- -C-	
F ₃ CO-	CH ₃ O- N=N- -C-	
F ₃ CO-	CH ₃ CH ₂ O- N=N- -C-	
F ₃ CO-	CH ₃ (CH ₂) ₂ O- N=N- -C-	
F ₃ CO-	CH ₃ (CH ₂) ₂ O- N=N- -C-	
F ₃ CO-	CH ₃ (CH ₂) ₂ O- N=N- -C-	
Br	CH ₃ O- N=N- -C-	
F ₃ C-	CH ₃ CH ₂ O- N=N- -C-	

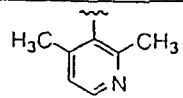
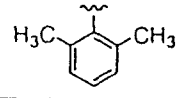
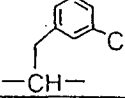
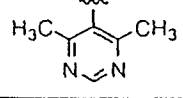
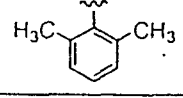
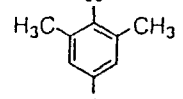
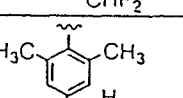
24 33
306

Br	-CH ₂ -	
Br	-CH ₂ -	
Br	-CH ₂ -	
Br	-CH ₂ -	
Br	-CH ₂ -	
Br	-CH ₂ -	
Br		
CH ₃ SO ₂ -		
Br		
Br		
F		
F		
F		

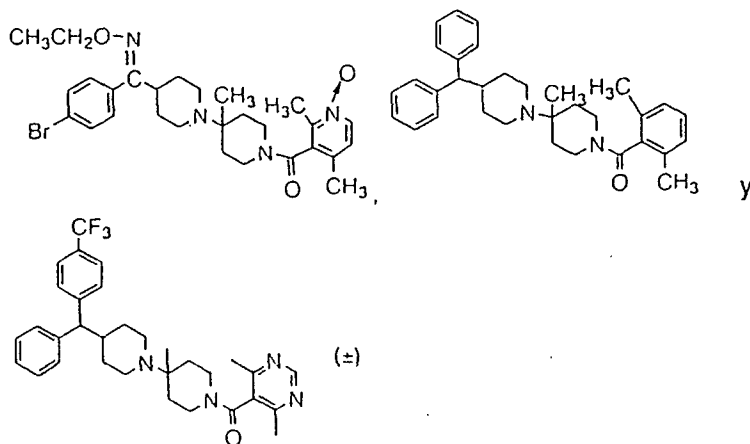
22 348
307

Br		
Cl		
F ₃ C-		
CH ₃ SO ₂ -		
CH ₃ SO ₂ -		
F ₃ CO-		
F ₃ CO-		
CH ₃ SO ₂ -		
CH ₃ SO ₂ -		
F ₃ C-		
F ₃ CO-		
F ₃ CO-		
F ₃ C-		

223 365
308

H			
F ₃ CO-			
F ₃ CO-			
F ₃ CO-			Enantiómero II
F ₃ CO-			Enantiómero II
F ₃ CO-			Enantiómero II

10. Un compuesto seleccionado del grupo que consiste en



11. Una composición farmacéutica para el tratamiento del Virus de Inmunodeficiencia Humana, rechazo de transplante de órganos sólidos, enfermedad de injerto versus huésped, artritis, artritis reumatoide, enfermedad inflamatoria del intestino, dermatitis atópica, psoriasis, asma, alergias, esclerosis

7/11/38
309

múltiple, que comprende una cantidad eficaz de un antagonista CCR5 de la reivindicación 1 en combinación con un portador farmacéuticamente aceptable.

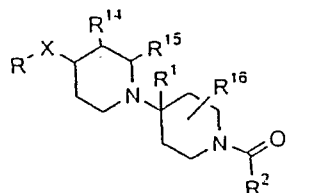
12. El uso de un compuesto de la reivindicación 1 para la preparación de un medicamento para tratar el Virus de Inmunodeficiencia Humana, rechazo a los trasplantes de órganos sólidos, enfermedad de injerto versus huésped, artritis, artritis reumatoide, enfermedad inflamatoria del intestino, dermatitis atópica, psoriasis, asma, alergias o esclerosis múltiple.

13. El uso de un compuesto de la reivindicación 1 para la preparación de un medicamento para uso combinado con uno o más de otros agentes antivirales útiles en el tratamiento del Virus de Inmunodeficiencia Humana.

14. El uso de la reivindicación 13 en el cual el agente antiviral está seleccionado del grupo que consiste en inhibidores de transcriptasa inversa nucleosídica, inhibidores de transcriptasa inversa no nucleosídica e inhibidores de proteasa.

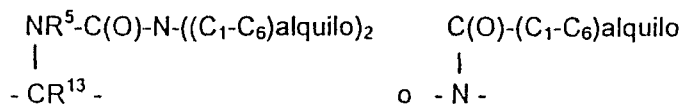
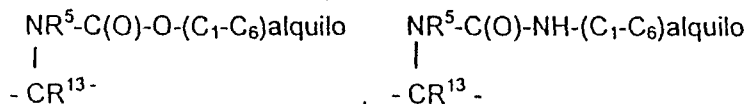
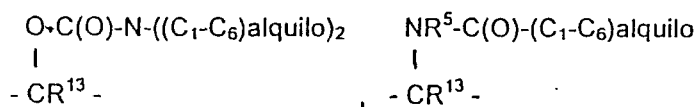
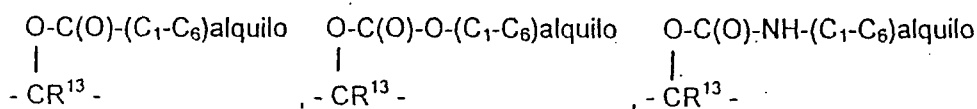
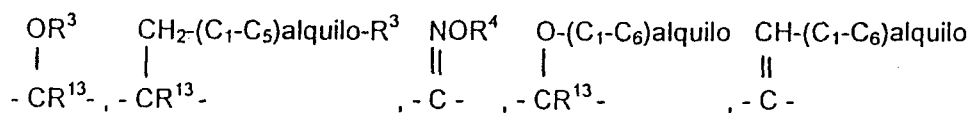
15. El uso de un compuesto de la reivindicación 1 para la preparación de un medicamento para uso combinado con uno o más agentes para tratar rechazo al trasplante de órganos sólidos, enfermedad de injerto versus huésped, enfermedad inflamatoria del intestino, artritis reumatoide o esclerosis múltiple.

16. El uso de un antagonista CCR5 de la fórmula I para la preparación de un medicamento para tratar el Virus de Inmunodeficiencia Humana, rechazo a los trasplantes de órganos sólidos, enfermedad de injerto versus huésped, artritis, artritis reumatoide, enfermedad inflamatoria del intestino, dermatitis atópica, psoriasis, asma, alergias o esclerosis múltiple, donde el antagonista CCR5 está representado por la fórmula estructural I:

28-37
310

o por una sal farmacéuticamente aceptable del mismo, donde

X es $-C(R^{13})_2-$, $-C(R^{13})(R^{19})-$, $-C(O)-$, $-O-$, $-NH-$, $-N((C_1-C_6)\text{alquilo})-$,



R es R^6 -fenilo, R^6 -piridilo, R^6 -tiofenilo o R^6 -naftilo;

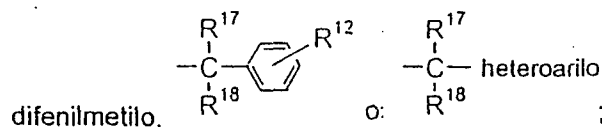
R^1 es hidrógeno, alquilo C_1-C_6 o alquenilo C_2-C_6 ;

R^2 es R^7 , R^8 , R^9 -fenilo; R^7 , R^8 , R^9 -heteroarilo substituido de 6 miembros;

R^7 , R^8 , R^9 -N-óxido de heteroarilo de 6 miembros substituido;

26748
311

R^{10} , R^{11} -heteroarilo substituido de 5 miembros; naftilo; fluorenilo;

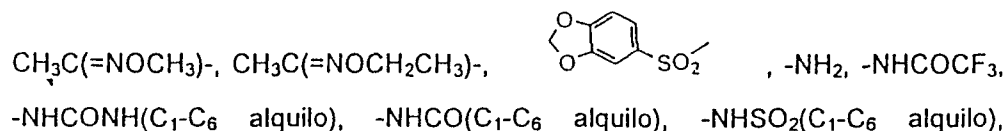


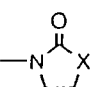
R^3 es R^6 -fenilo, R^6 -heteroarilo o R^6 -naftilo;

R^4 es hidrógeno, alquilo C_1-C_6 , flúor- C_1-C_6 alquilo, ciclopropilmetilo, $-CH_2CH_2OH$, $-CH_2CH_2O-(C_1-C_6)$ alquilo, $-CH_2C(O)-O-(C_1-C_6)$ alquilo, $-CH_2C(O)-NH_2$, $-CH_2C(O)-NH(C_1-C_6)$ alquilo o $-CH_2C(O)-N((C_1-C_6)$ alquilo) $_2$;

R^5 y R^{11} están independientemente seleccionados del grupo que consiste en hidrógeno y (C_1-C_6) -alquilo;

R^6 representa de 1 a 3 substituyentes independientemente seleccionados del grupo que consiste en hidrógeno, halógeno, alquilo C_1-C_6 , alcoxi C_1-C_6 , $-CF_3$, CF_3O- , $CH_3C(O)-$, $-CN$, CH_3SO_2- , CF_3SO_2- , R^{14} -fenilo, R^{14} -bencilo,



heteroarilo de 5 miembros y , donde X es $-O-$, $-NH-$ o $-N(CH_3)-$;

R^7 y R^8 están independientemente seleccionados del grupo que consiste en (C_1-C_6) alquilo, halógeno, $-NR^{20}R^{21}$, $-OH$, $-CF_3$, $-OCH_3$, $-O$ -acilo, y $-OCF_3$;

R^9 es R^7 , hidrógeno, fenilo, $-NO_2$, $-CN$, $-CH_2F$, $-CHF_2$, $-CHO$, $-CH=NOR^{20}$, piridilo, N-óxido piridilo, pirimidinilo, pirazinilo, $-N(R^{20})CONR^{21}R^{22}$, $-NHCONH(\text{cloro-}(C_1-C_6)\text{alquilo})$, $-NHCONH((C_3-C_{10})\text{cicloalquilo}(C_1-C_6)\text{alquilo})$, $-NHCO(C_1-C_6)$ alquilo, $-NHCOCF_3$, $-NHSO_2N((C_1-C_6)\text{alquilo})_2$, $-NHSO_2(C_1-C_6)$ alquilo, $-N(SO_2CF_3)_2$, $-NHCO_2(C_1-C_6)$ alquilo, C_3-C_{10} cicloalquilo, $-SR^{23}$, $-SOR^{23}$, $-SO_2R^{23}$, $-SO_2NH(C_1-C_6)$ alquilo), $-OSO_2(C_1-C_6)$ alquilo, $-OSO_2CF_3$, hidroxil- $(C_1-$

72749
312

C₆)alquilo, -CON R²⁰R²¹, -CON(CH₂CH₂O-CH₃)₂, -OCONH(C₁-C₆)alquilo, -CO₂R²⁰, -Si(CH₃)₃ o -B(OC(CH₃)₂)₂;

R¹⁰ es (C₁-C₆)alquilo, -NH₂ o R¹²-fenilo;

R¹² representa de 1 a 3 sustituyentes independientemente seleccionados del grupo que consiste en hidrógeno, (C₁-C₆)alquilo, -CF₃, -CO₂R²⁰, -CN, (C₁-C₆)alcoxi y halógeno;

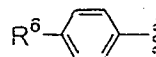
R¹³, R¹⁴, R¹⁵ y R¹⁶ están independientemente seleccionados del grupo que consiste en hidrógeno y (C₁-C₆)alquilo;

R¹⁷ y R¹⁸ están independientemente seleccionados del grupo que consiste en hidrógeno y alquilo C₁-C₆, o R¹⁷ y R¹⁸ conjuntamente son un grupo alquileo C₂-C₅ y con el carbono al cual están unidos forman un anillo espiro de 3 a 6 átomos de carbono;

R¹⁹ es R⁶-fenilo, R⁶-heteroarilo, R⁶-naftilo, cicloalquilo C₃-C₁₀, (C₃-C₁₀)cicloalquil(C₁-C₆)alquilo o (C₁-C₆)alcoxi(C₁-C₆)alquilo;

R²⁰, R²¹ y R²² están independientemente seleccionados del grupo que consiste en H y alquilo C₁-C₆; y

R²³ es alquilo C₁-C₆ o fenilo.



17. El uso de la reivindicación 16 donde R es

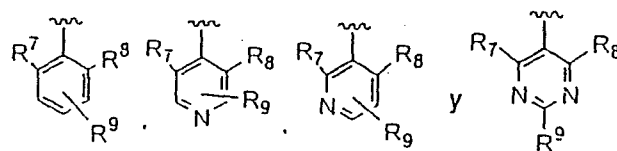
18. El uso de la reivindicación 16, en el cual X es -CHOR³, -C(R¹³)(R¹⁹)- o -C(=NOR⁴).

19. El uso de la reivindicación 18, donde R³ es piridilo, R⁴ es alquilo (C₁-C₆), o R¹³ es hidrógeno y R¹⁹ es R⁶-fenilo.

20. El uso de la reivindicación 16, donde R² es R⁷, R⁸, R⁹-fenilo; R⁷, R⁸, R⁹-piridilo o un N-óxido del mismo; o R⁷, R⁸, R⁹-pirimidilo.

21. El uso de la reivindicación 20, donde R² está seleccionado del grupo que consiste en

313



donde R^7 y R^8 están seleccionados del grupo que consiste en (C_1-C_6) alquilo, halógeno, y $-NH_2$, y R^9 es hidrógeno.

22. El uso de la reivindicación 16 para el tratamiento del Virus de Inmunodeficiencia Humana que comprende además uno o más de otros agentes antivirales que son útiles para el tratamiento del Virus de Inmunodeficiencia Humana.

23. El uso de la reivindicación 22 donde el agente antiviral está seleccionado del grupo que consiste en inhibidores de transcriptasa inversa nucleosídica, inhibidores de transcriptasa inversa no nucleosídica e inhibidores de proteasa.

24. El uso de la reivindicación 16 para el tratamiento del rechazo al trasplante de órganos sólidos, enfermedad de injerto versus huésped, enfermedad inflamatoria del intestino, artritis reumatoide o esclerosis múltiple, que comprende además uno o más de otros agentes que son útiles en el tratamiento de dichas enfermedades.

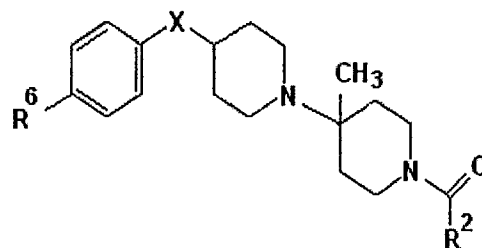
25. Una presentación que comprende en recipientes separados en un paquete único, composiciones farmacéuticas que se usan en combinación para tratar el virus de Inmunodeficiencia Humana que comprende en un recipiente una composición farmacéutica que comprende una cantidad eficaz de un antagonista CCR5 de la reivindicación 16 en un portador farmacéuticamente aceptable, y en recipientes separados, una o más composiciones farmacéuticas que comprenden una cantidad eficaz de un agente antiviral u otro agente que es

27/37
314

Útil en el tratamiento del virus de Inmunodeficiencia Humana en un portador farmacéuticamente aceptable.

26. Una composición farmacéutica que comprende un compuesto de formula II, de acuerdo a la reivindicación 1, donde dicha composición es una crema.

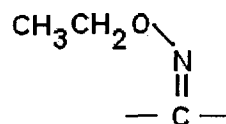
27. Una composición farmacéutica de acuerdo con la reivindicación 26, donde el compuesto activo es,



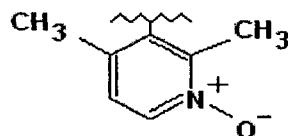
donde R^6 es,

Br

X es,



y R^2 es,



ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

30 37
315

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 05 - 977
FECHA : ENERO 6 DE 2005

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00031252 00000004

Folios: 31

Fecha (AMD): 2005-01-07 15:49:05

Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEME

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

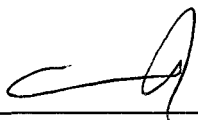
DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JOSE SANTOS	CONSIGNACION	BANCO POPULAR	050-00110-6	29810435	04/01/2005	16,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	4,000.00
		TOTAL :	\$ 4,000.00

SON: CUATRO MIL PESOS

RESPONSABLE :



RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

316

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 98,594
FECHA : DICIEMBRE 22 DE 2004

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00031252 00000004 Folios: 31
Fecha (AND): 2005-01-07 15:49:05
Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
JHON BULLA	CONSIGNACION	BANCO POPULAR	050-00110-6	37958998	22/12/2004	1,354,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
12		MARCAS Y LEMAS COMERCIALES	87,000.00
		TOTAL :	\$ 87,000.00

SON: OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

317
328

375
2005-07-14

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

Doctor
Carlos Olarte
Apoderado

Oficio N° 00005814

REFERENCIA

Radicación	00 31252
Trámite	002
Evento	001
Actuación	430
Folios	019

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 31252, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 110-145
- . Ejemplos: folios 145-217
- . Capítulo reivindicatorio estudiado: 295-324
- . Se reivindica prioridad presentada en Estados Unidos, el 04.05.99, bajo el número 09/305187

Objeto de la invención

Según las reivindicaciones 1 a 27 de la presente solicitud, se refiere a derivados de piperidina o sus sales farmacéuticamente aceptables, cuyos sustituyentes se revelan en la descripción y que son antagonistas de CCR5; dichos compuestos son útiles en el tratamiento de VIH, trasplante de órganos. Finalmente se revelan combinaciones de los compuestos de la presente solicitud con agentes antivirales para el tratamiento del VIH

Clasificación internacional de patentes A 61 K 31/495

Claridad de la solicitud

De la decisión 486 establece que "Las reivindicaciones definirán la materia que se proteger mediante la patente. Deben ser claras y concisas y estar enteramente basadas por la descripción"

318

Teniendo en cuenta lo anterior, la definición de R2 en la reivindicación 1 no es claro, porque R2 puede ser R7, R8, R9-fenilo o R2 puede ser R7-fenilo, R8-fenilo o R9-fenilo.

La reivindicación 10 no puede ser independiente

Favor hacer las aclaraciones y correcciones del caso.

Excepciones a la patentabilidad

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"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"*

Teniendo en cuenta lo anterior, el contenido de las reivindicaciones 12-24 que trata de "el uso de un compuesto de la reivindicación 1...", no es patentable, debido a que los usos no son objeto de patente de acuerdo a la legislación vigente.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 04.05.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	WO 9805292	"Antagonistas muscarínicos"	12.02.98
2	WO 9806697	"Antagonistas de éter muscarínicos"	19.02.98
3	WO 9801425	"Piperidinas 1,4-disustituidas como agonistas muscarínicos"	15.01.98

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"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 del artículo 14 de la decisión 486 de la comisión de la comunidad andina, 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 artículo 16 de la decisión 486 contempla que *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La publicación WO 9805292 se refiere a compuestos derivados de piperidina de fórmula (I), cuyos sustituyentes se revelan en la descripción, son antagonistas muscarínicos. Se publican además composiciones farmacéuticas que los contienen.

319
316

La publicación WO 9806697 revela piperidinas 1,4-di sustituidas de fórmula (I) que son antagonistas muscarínicos, se mencionan sus métodos de síntesis y composiciones farmacéuticas que los contienen.

La publicación WO 9801425 revela piperidinas 1,4-di sustituidas de fórmula (I) que son antagonistas muscarínicos, se mencionan sus métodos de síntesis y composiciones farmacéuticas que los contienen.

Comparando elemento por elemento, los compuestos de la presente solicitud son iguales a los de las anterioridades citadas y pueden afectar la novedad de la presente solicitud.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9805292	1-11, 25-27	Novedad
2	WO 9806697	1-11, 25-27	Novedad
3	WO 9801425	1-11, 25-27	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 la 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.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001

Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 14 JUL. 2005

CONCEPTO TÉCNICO Número 1003	EXAMINADOR TÉCNICO Código 202024
---------------------------------	-------------------------------------



381
320

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

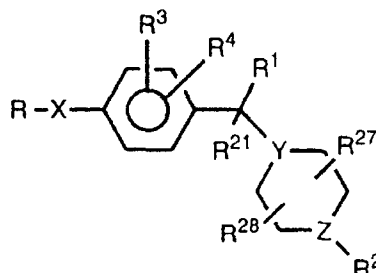
(51) International Patent Classification ⁶ : A61K	A2	(11) International Publication Number: WO 98/05292 (43) International Publication Date: 12 February 1998 (12.02.98)
(21) International Application Number: PCT/US97/13383 (22) International Filing Date: 6 August 1997 (06.08.97) (30) Priority Data: 08/700,628 8 August 1996 (08.08.96) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). (72) Inventors: LOWE, Derek, B.; 237 North 9th Street, Kenilworth, NJ 07033 (US). CHANG, Wei, K.; 63 West Cedar Street, Livingston, NJ 07039 (US). KOZLOWSKI, Joseph, A.; P.O. Box 7391, Princeton, NJ 08543-7391 (US). BERGER, Joel, G.; 5675 North Camino Esplandora, Tucson, AZ 85718 (US). McQUADE, Robert; 221 Mountainview Avenue, Scotch Plains, NJ 07076 (US). BARNETT, Allen; 13 Flanders Drive, Pine Brook, NJ 07058 (US). SHERLOCK, Margaret; 34 Parkway West, Bloomfield, NJ 07003 (US). TOM, Wing; 133 Cedar Grove Parkway, Cedar Grove, NJ 07009 (US). DUGAR, Sundee; 749 Wingate Drive, Bridgewater, NJ 08807 (US). CHEN, Lian-Yong; 10 Pond View Drive, Plainsboro, NJ 08536 (US). CLADER, John, W.; 428 North Union Avenue, Cranford, NJ 07016 (US). CHACKALAMANNIL, Samuel; 79 Stratford Road, East Brunswick, NJ 08816 (US). WANG,		Yuguang; 38 Princess Drive, North Brunswick, NJ 08902 (US). McCOMBIE, Stuart, W.; 28 Hanford Place, Caldwell, NJ 07006 (US). TAGAT, Jayaram, R.; 133 Boynton Court, Westfield, NJ 07090 (US). VICE, Susan, F.; 1144 Sawmill Road, Mountainside, NJ 07092 (US). VACCARO, Wayne, D.; 1706 Westover Road, Yardley, PA 19067 (US). GREEN, Michael, J.; 1146 Rancho Encinitas Drive, Encinitas, CA 92024 (US). BROWNE, Margaret, E.; 26 Highfield Road, Bloomfield, NJ 07003 (US). ASBEROM, Theodoros; 525 Eagle Rock Avenue, West Orange, NJ 07052 (US). BOYLE, Craig, D.; 180 Northfield Road, Bridgewater, NJ 08807 (US). JOSIEN, Hubert, B.; 5441 Washington Boulevard, Jersey City, NJ 07310 (US). (74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). (81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), 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 Without international search report and to be republished upon receipt of that report.
(54) Title: MUSCARINIC ANTAGONISTS (I) (57) Abstract Di-N-substituted piperazine or 1,4 di-substituted piperidine compounds in accordance with formula I (including all isomers, salts, esters, and solvates) wherein R, R¹, R², R³, R⁴, R²¹, R²⁷, R²⁸, X, Y and Z as defined herein are muscarinic antagonists useful for treating cognitive disorders such as Alzheimer's disease. Pharmaceutical compositions and methods of preparation are also disclosed. Also disclosed are synergistic combinations of compounds of the above formula with acetylcholinesterase inhibitors.		

321

-148-

What is Claimed:

1. A compound having the structural formula

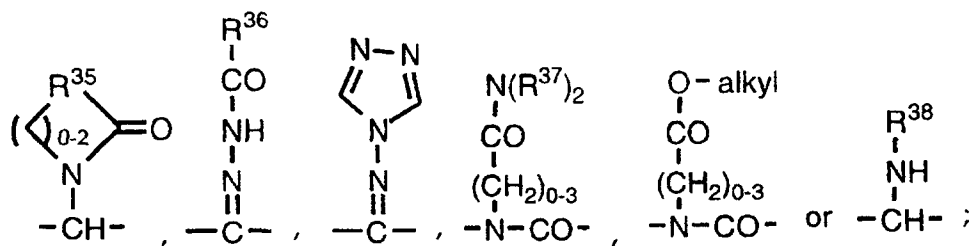
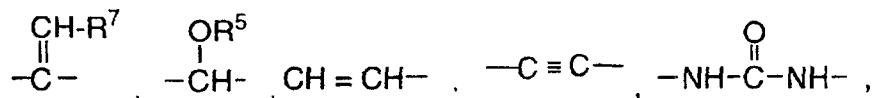
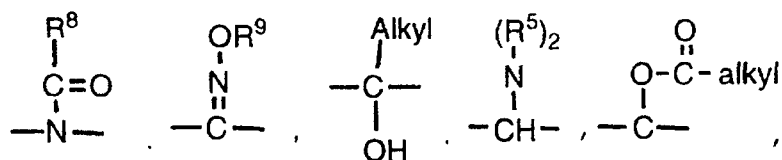


- 5 including all isomers and pharmaceutically acceptable salts, esters, and solvates thereof,

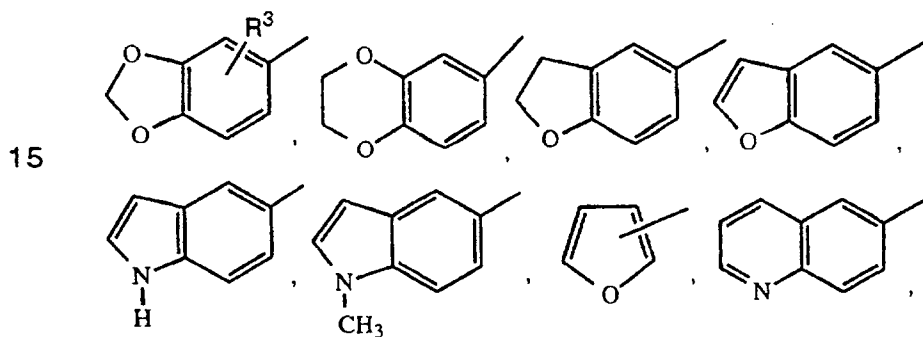
wherein one of Y and Z is N and the other is N, CH, or C-alkyl;

X is -O-, -S-, -SO-, -SO₂-, -NR⁶-, -CO-, -CH₂-, -CS-, -C(OR⁵)₂-,
-C(SR⁵)₂-, -CONR²⁰-, -C(alkyl)₂-, -C(H)(alkyl)-, -NR²⁰-SO₂-,

- 10 -SO₂-NR²⁰-, -NR²⁰CO-, -O-CO-NH-, -NH-CO-O-,

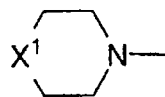
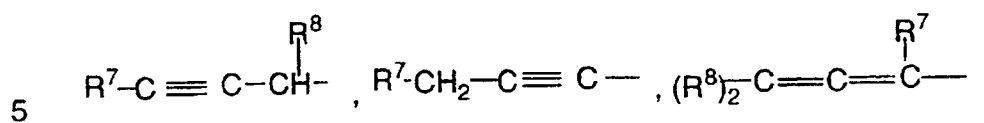
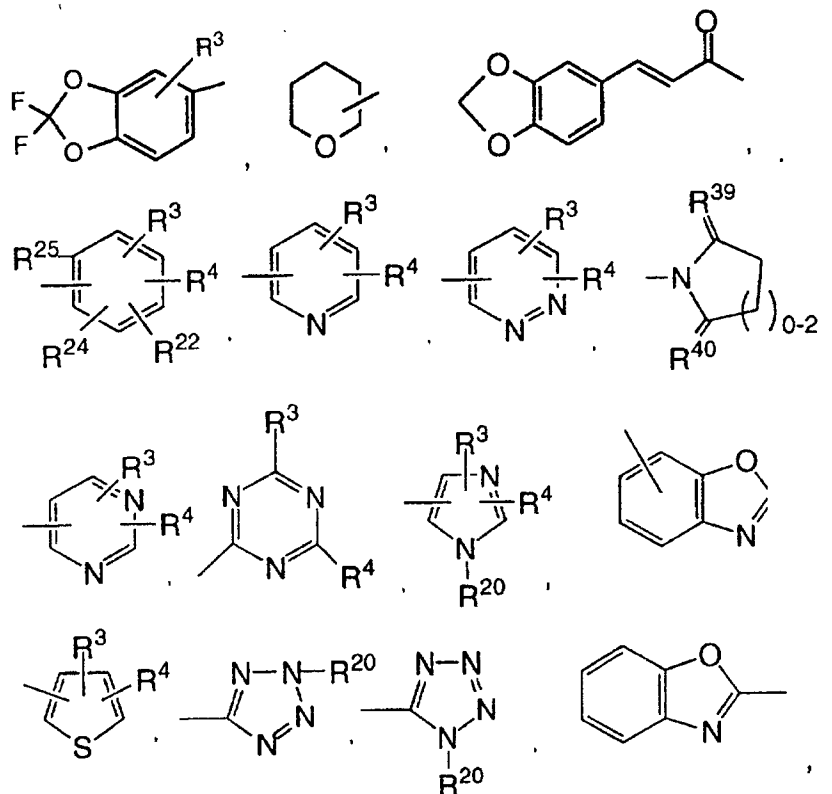
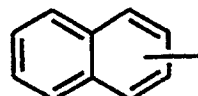
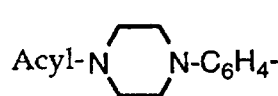
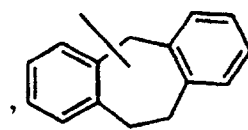
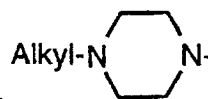
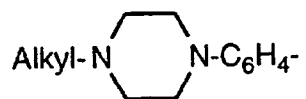
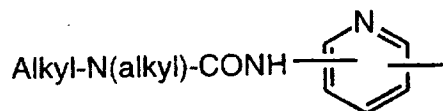
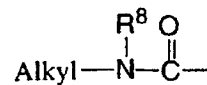
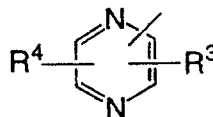
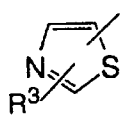
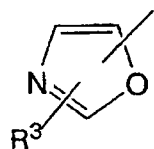


R is



322
349

-149-

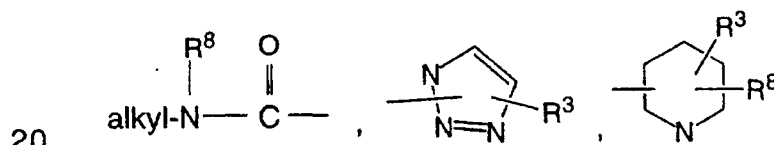
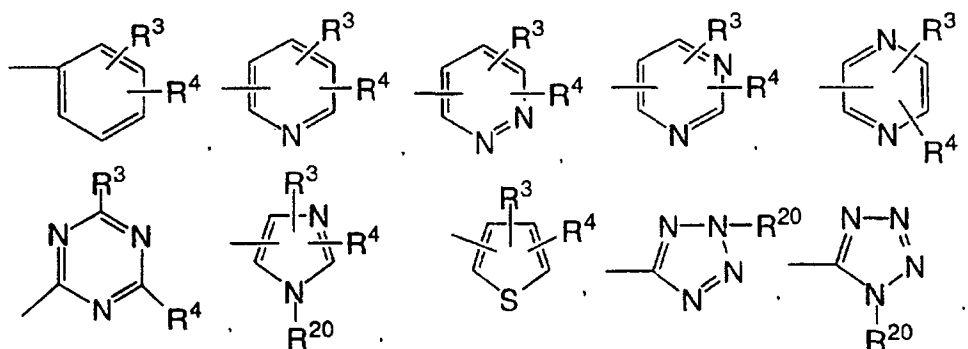
(wherein X¹ is -CH₂-, -O-, or -NR⁷-),

hydrogen, acyl, alkyl, alkoxy, alkenyl, cycloalkyl, cycloalkyl substituted with one or two groups selected from the group consisting of alkyl and carbonyl, cycloalkenyl, bicycloalkyl, arylalkenyl, benzyl, benzyl substituted with up to three independently selected R³ groups,

5 cycloalkylalkyl, polyhaloacyl, benzyloxyalkyl, hydroxyC₂-C₂₀alkyl, alkenylcarbonyl, alkylarylsulfonyl, alkoxycarbonylaminoacyl, alkylsulfonyl, or arylsulfonyl, additionally, when X is -CH₂-, R may also be -OH; in further addition, when X is not N, R may also be

hydroxymethyl, in further addition, R and X may combine to form the group Prot-(NOAA)_r-NH- wherein r is an integer of 1 to 4, Prot is a nitrogen protecting group and when r is 1, NOAA is a naturally occurring amino acid or an enantiomer thereof, or when r is 2 to 4, each NOAA is a peptide of an independently selected naturally occurring amino acid or an enantiomer thereof;

15 R¹ and R²¹ are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, alkynyl, cyano, aminoalkyl, alkoxycarbonyl, aminocarbonyl, hydroxyamidino, alkoxycarbonylalkyl, phenyl alkyl, alkylcarbonyloxyalkyl,



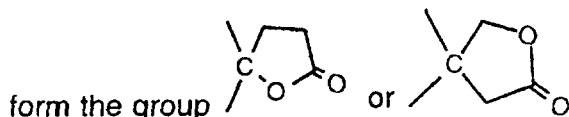
H, —OH, (provided R¹ and R²¹ are both not —OH and Y is not N), formyl, —CO alkyl, —COacyl, —COaryl, and hydroxyalkyl; additionally R¹ and R²¹ together may form the group =CH₂, =N-OR⁵, =N-CN, =N-N(R⁵)₂,

=CH-alkyl, alkylene, $\overset{\text{alkyl}}{\underset{|}{\text{=C}}}$ -alkyl or =C(halo)₂; in further addition, R¹

331
324

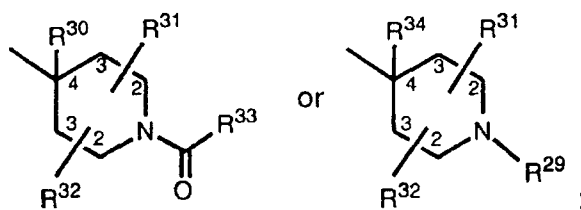
-151-

and R²¹ together with the carbon atom to which they are attached may



- or R¹ and R²¹ together with the carbon atom to which they are attached may form a saturated heterocyclic ring containing 3 to 7 carbon atoms, one or more of which may be optionally substituted by alkyl, and one or two groups independently selected from S, O, and N-R²⁰;

R² is



- R³, R⁴, R²², R²⁴, and R²⁵ are independently selected from the group consisting of alkyl, H, halo, alkoxy, benzyloxy, benzyloxy substituted by nitro or aminoalkyl, haloalkyl, polyhaloalkyl, nitro, cyano, sulfonyl, hydroxy, amino, alkylamino, formyl, alkylthio, polyhaloalkoxy, acyloxy, trialkylsilyl, alkylsulfonyl, arylsulfonyl, acyl, alkoxycarbonyl, alkylsulfinyl; -OCONH₂, -OCONH-alkyl, alkylaminoalkyl, dialkylaminoalkyl, -COOH, -CON(R²⁰)₂, -OCON(alkyl)₂, -NHCOO-alkyl, -NHCO-alkyl, phenyl, hydroxyalkyl, or morpholino;

- each R⁵ and R⁶ is independently selected from the group consisting of H and alkyl, provided that when X is C(OR⁵)₂ or C(SR⁵)₂, both R⁵ groups cannot be H, and in addition, when X is C(OR⁵)₂ or C(SR⁵)₂, the two R⁵ groups in X may be joined to form -(CR²⁰)_p- wherein p is an integer of 2 to 4;

R⁷ is independently selected from the group consisting of H, alkyl, arylalkyl, cycloalkyl, aryl and aryl substituted with R³ and R⁴ as defined herein;

- each R⁸ is independently selected from the group consisting of H, hydroxyalkyl or alkyl, or two R⁸ groups may be joined to form an alkylene group;

R⁹ is H, alkyl, aralkyl, or acyl;

R²⁰ is H, aryl or alkyl;

737
325

-152-

R^{27} and R^{28} are independently selected from the group consisting of H, alkyl, hydroxyalkyl, arylalkyl, aminoalkyl, haloalkyl, thioalkyl, alkylthioalkyl, carboxyalkyl, imidazolyalkyl, and indolyalkyl; or R^{27} and R^{28} may combine to form an alkylene group;

5 R^{29} is H, alkyl, -CO-alkyl, -CO-cycloalkyl, alkoxy carbonyl, amino-carbonyl, aryloxy carbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, arylsulfonyl or -SO₂-NH- R^{20} ;

R^{30} is H, alkyl, aryl, cycloalkyl, hydroxyalkyl, aminoalkyl, -COOR²⁰, -CON(R^{20})₂ or cyano;

10 R^{31} and R^{32} are the same as R^{30} and in addition, two R^{30} , R^{31} and R^{32} groups may form the group -(CH₂)_r- (wherein r is 1 to 6), in further addition, R^{31} and R^{32} can also be hydroxy, -N(R^{20})₂, -O-acyl, -N(R^{20})acyl, -OCOOR²⁰, or -OCON(R^{20})₂;

15 R^{33} is aryl or heteroaryl, with the proviso that when R^{33} is heteroaryl, the CO- R^{33} bond is to a carbon atom in the R^{33} group;

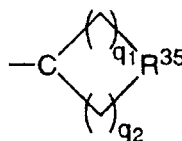
R^{34} is alkyl, cycloalkyl or aryl and in addition R^{34} may also be H when R^1 and R^{21} together with the carbon atom to which they are attached form a saturated heterocyclic ring containing 3 to 7 carbon atoms and two groups independently selected from S, O, and N- R^{20} ;

20 R^{35} is -CH₂-, -NR²⁰- or -O-;

R^{36} is -NH₂, alkyl or alkoxy;

R^{37} is independently selected from the group consisting of H and alkyl;

R^{38} is -CO-(CH₂)₀₋₅-OR⁵, -SO₂-(alkyl), or



25 wherein q_1 and q_2 are independently 1-5, provided that the sum of q_1 and q_2 is 2-5; and

R^{39} and R^{40} are independently selected from the group consisting of =O and (H,H).

30

2. A compound of claim 1 wherein Y and Z are N

3. A compound of claim 1 wherein Y is CH and Z is N

33
326

-154-

37, 41, 43, 44, 49, 53, 54, 56, 57, 58, 59, 80, 82, 84, 85, 94, 98, 100, 108, 121, 126, 127, 137, 145, 151, 152, 154, 155, 162, 166, 178, 179, 181, 185, 190, 191, 194, 199, 214, 215, 216, 225, 247, 253, 256, 257, 337, 339, 340, 341, 349, 351, 367, 409, 459, 479, 488, 489, 490, 500, 501, 502, 503, 505, 506, 507, 515, 516, 517, 555 and 562 from the tables of compounds appearing in the specification.

10. A pharmaceutical composition which comprises a compound as defined in claim 1 in combination with a pharmaceutically acceptable carrier.
11. A process for the preparation of a pharmaceutical composition as defined in claim 10 comprising admixing a compound as claimed in any of claims 1 to 9 with a pharmaceutically acceptable carrier.
12. The use of a compound of claim 1 for the preparation of a medicament for treating a cognitive or neurodegenerative disease.
13. A kit for treating a cognitive or neurodegenerative disease comprising in separate containers in a single package pharmaceutical compounds for use in combination, in one container a compound in accordance with claim 1 and in a separate container an acetylcholinesterase inhibitor, said compound and inhibitor each being in a pharmaceutically acceptable carrier and their combined quantities being an effective amount.
14. A method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a compound of claim 1, alone or in combination with an acetylcholinesterase inhibitor.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



327

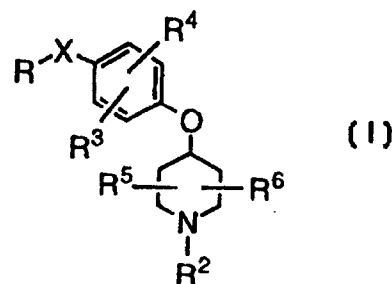
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 211/46, 405/12, 405/14, 211/58, A61K 31/445	A1	(11) International Publication Number: WO 98/06697 (43) International Publication Date: 19 February 1998 (19.02.98)
(21) International Application Number: PCT/US97/13894 (22) International Filing Date: 13 August 1997 (13.08.97) (30) Priority Data: 08/700,722 15 August 1996 (15.08.96) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors: WANG, Yuguang; 38 Princess Drive, North Brunswick, NJ 08902 (US). CHANG, Wei, K.; 63 West Cedar Street, Livingston, NJ 07039 (US). DUGAR, Sundeep; 749 Wingate Drive, Bridgewater, NJ 08807 (US). CHACKALAMANNIL, Samuel; 79 Stratford Road, East Brunswick, NJ 08816 (US). (74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), 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 With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ETHER MUSCARINIC ANTAGONISTS

(57) Abstract

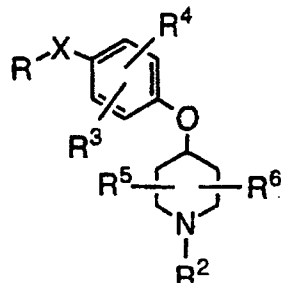
1,4 Di-substituted piperidine muscarinic antagonists of formula (I) or an isomer, pharmaceutically acceptable salt, ester or solvate thereof, wherein X is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -C(OR⁷)₂-, -CH₂-O-, -O-CH₂-, -CH=CH-, -CH₂-, -CH(C₁-C₆ alkyl)-, -C(C₁-C₆ alkyl)₂-, -CONR¹⁷-, -NR¹⁷CO-, -O-C(O)NR¹⁷-, -NR¹⁷C(O)-O-, -SO₂NR¹⁷- or -NR¹⁷SO₂-; R is cycloalkyl, optionally substituted phenyl or optionally substituted pyridyl; R² is H, alkyl, optionally substituted cycloalkyl, cycloalkenyl, t-butoxycarbonyl or optionally substituted piperidinyl; and the remaining variables are as defined in the specification, are disclosed. Compounds of formula (I) are useful for treating cognitive disorders such as Alzheimer's disease. Also disclosed are pharmaceutical compositions, methods of preparation and combinations of compounds of formula (I) with ACh'ase inhibitors.



335
328

What is Claimed:

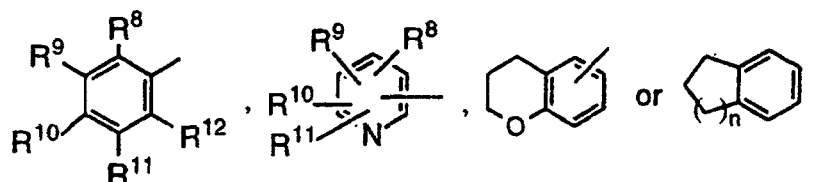
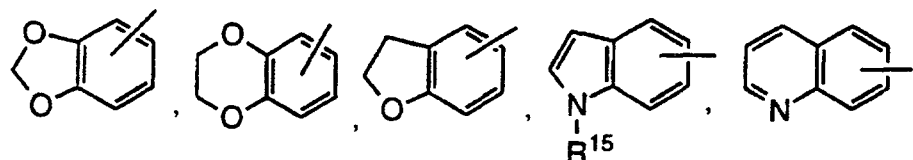
1. A compound having the structural formula



or an isomer, pharmaceutically acceptable salt, ester or solvate thereof,
wherein

X is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -C(OR⁷)₂-, -CH₂-O-, -O-CH₂-, -CH=CH-, -CH₂-, -CH(C₁-C₆ alkyl)-, -C(C₁-C₆ alkyl)₂-, -CONR¹⁷-, -NR¹⁷CO-, -O-C(O)NR¹⁷-, -NR¹⁷C(O)-O-, -SO₂NR¹⁷- or -NR¹⁷SO₂-;

R is C₃-C₆ cycloalkyl,



n is 1, 2 or 3;

R² is H, C₂-C₇ alkyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl substituted by 1 to 4 groups independently selected from R¹⁸, C₃-C₆ cycloalkenyl, t-

- 15 butoxycarbonyl or

R³ and R⁴ are independently selected from the group consisting of H, halo, -CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy and -OH;

- 20 R⁵ and R⁶ are independently selected from the group consisting of H, C₁-C₆ alkyl, -CF₃, C₁-C₆ alkoxy, -OH, C₁-C₆ alkylcarbonyl, C₁-C₆ alkoxy carbonyl, R¹³CONH-, (R¹³)₂NCO-, R¹³OCONH-, R¹³NHCONH- and NH₂CONR¹³-;

R⁷ is independently selected from the group consisting of C₁-C₆ alkyl; or the two R⁷ groups may be joined to form -(C(R¹⁴)₂)_p- wherein p is an integer from 2 to 4;

34
329

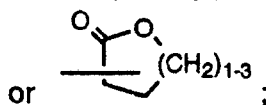
R⁸, R⁹, R¹⁰, R¹¹ and R¹² are independently selected from the group consisting of H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, benzyloxy, benzyloxy substituted by -NO₂ or -N(R¹⁴), halo C₁-C₆ alkyl, polyhalo C₁-C₆ alkyl, -NO₂, -CN, -SO₂, -OH, -NH₂, -N(R¹⁴)₂, -CHO, polyhalo C₁-C₆ alkoxy, acyloxy, (C₁-C₄ alkyl)₃Si-, (C₁-C₆ alkyl)SO₀₋₂, arylsulfonyl, heteroaryl-sulfonyl, acyl, (C₁-C₆ alkoxy)CO-, -OCON(R¹⁴)₂, -NHCOO-(C₁-C₆)alkyl, -NHCO-(C₁-C₆ alkyl), phenyl, hydroxy(C₁-C₆ alkyl) or morpholino;

R¹³ is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -(C₁-C₆ alkyl)COOR¹⁵, aryl, heteroaryl, -(C₁-C₆ alkyl)aryl, -(C₁-C₆ alkyl)heteroaryl and adamantyl;

R¹⁴ is independently selected from the group consisting of H and C₁-C₆ alkyl;

R¹⁵ is independently selected from the group consisting of H, C₁-C₂₀ alkyl, C₃-C₆ cycloalkyl, aryl substituted by 1 to 3 groups independently selected from R³ and heteroaryl substituted by 1 to 3 groups independently selected from R³;

R¹⁶ is H, C₁-C₆ alkyl, -COR²⁰, C₁-C₆ alkoxy carbonyl, -CON(R¹⁴)₂, -CONH(R³-aryl), -SO₁₋₂-R¹⁵, -SO₁₋₂-(CH₂)_m-R²¹, -SON(R¹⁴)₂, -COSR¹⁴



R¹⁷ is H, C₁-C₆ alkyl, aryl or heteroaryl;

R¹⁸ is independently selected from the group consisting of halo, -CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy, -OH, =O, -CON(R¹⁴)₂ and -N(R¹⁴)COR¹⁵;

R¹⁹ is H, -OH, C₁-C₂₀ alkyl, C₃-C₆ cycloalkyl, aryl substituted by 1 to 3 groups independently selected from R³ or heteroaryl substituted by 1 to 3 groups independently selected from R³;

R²⁰ is H, C₁-C₂₀ alkyl, C₁-C₆ alkoxy(C₁-C₆)alkyl, C₃-C₆ cycloalkyl, aryl, aryl(C₁-C₆ alkyl)-, aryloxy, aryloxy(C₁-C₆ alkyl)-, tetrahydrofuranyl or heteroaryl, wherein the aryl or heteroaryl group is substituted by 1 to 3 groups independently selected from R³;

m is 0 to 3; and

R²¹ is C₇-C₁₀ bridged cycloalkyl or C₇-C₁₀ bridged cycloalkyl wherein the cycloalkyl portion is substituted by 1 or 2 substituents selected from the group consisting of C₁-C₆ alkyl or =O.

2. A compound of claim 1 wherein X is -S-, -SO-, -SO₂- or -CH₂-.

337
330

8. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 7, alone or in combination with an acetylcholinesterase inhibitor, in combination with a pharmaceutically acceptable carrier.
9. The use of a compound of any of claims 1 to 7, alone or in combination with an acetylcholinesterase inhibitor, for the preparation of a medicament for treating a cognitive or neurodegenerative disease.
10. A process for preparing a pharmaceutical composition as defined in claim 9 comprising admixing a compound of any of claims 1 to 7, alone or in combination with an acetylcholinesterase inhibitor, with a pharmaceutically acceptable carrier.
11. A kit for treating a cognitive or neurodegenerative disease comprising in separate containers in a single package pharmaceutical compounds for use in combination, in one container a compound in accordance with any of claims 1 to 7 and in a separate container an acetylcholinesterase inhibitor, said compound and inhibitor each being in a pharmaceutically acceptable carrier and their combined quantities being an effective amount.
12. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a compound of any of claims 1 to 7, alone or in combination with an acetylcholinesterase inhibitor.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

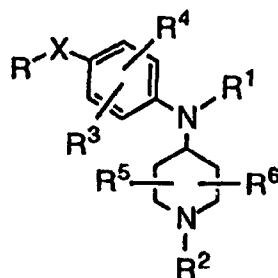


331

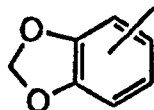
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 211/58, 405/12, 405/14, A61K 31/445	A1	(11) International Publication Number: WO 98/01425 (43) International Publication Date: 15 January 1998 (15.01.98)
(21) International Application Number: PCT/US97/11176 (22) International Filing Date: 8 July 1997 (08.07.97) (30) Priority Data: 08/678,618 10 July 1996 (10.07.96) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors: ASBEROM, Theodoros; 525 Eagle Rock Avenue, West Orange, NJ 07052 (US). LOWE, Derek, B.; 237 North 9th Street, Kenilworth, NJ 07033 (US). GREEN, Michael, J.; 1146 Rancho Encinitas Drive, Encinitas, CA 92024 (US). (74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), 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>

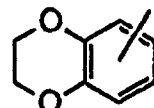
(54) Title: **1,4-DI-SUBSTITUTED PIPERIDINES AS MUSCARINIC ANTAGONISTS**



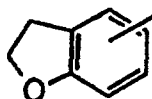
(I)



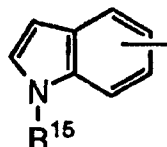
(a)



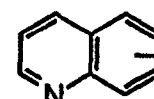
(b)



(c)



(d)



(e)

(57) Abstract

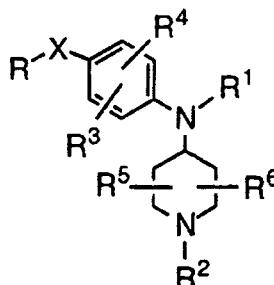
1,4-Di-substituted piperidine muscarinic antagonists of formula (I) or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein X is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -C(OR⁷)₂-, -CH₂-O-, -O-CH₂-, -CH=CH-, -CH₂-, -CH(C₁-C₆ alkyl)-, -C(C₁-C₆ alkyl)₂-, -CONR¹⁷-, -NR¹⁷CO-, -SO₂NR¹⁷- or -NR¹⁷SO₂-; R is C₃-C₆ cycloalkyl, (a), (b), (c), (d), (e), optionally substituted phenyl or optionally substituted pyridyl; R¹ is H, -CN, -CF₃, alkyl, cycloalkyl, cycloalkenyl, alkenyl, -COR¹⁵, -COO(alkyl), aryl, heteroaryl, alkylaryl or alkylheteroaryl, alkylaryl, alkylheteroaryl or -CON(R¹³)₂; R² is cycloalkyl, cycloalkenyl, t-butoxycarbonyl or optionally substituted 4-piperidinyl; R³ and R⁴ are H, halo, -CF₃, alkyl, alkoxy or -OH; R⁵ and R⁶ are H, alkyl, -CF₃, alkoxy, -OH, alkylcarbonyl, alkoxy carbonyl, R¹³CONH-, R¹⁴OCONH-, R¹⁵NHCONH- or NH₂CONR¹³-; R⁷ is H or alkyl, or the two R⁷ groups may form -(CH₂)₂-4; R¹³ is H, alkyl, cycloalkyl, -(alkyl)COOR¹⁵, aryl, heteroaryl, alkylaryl, alkylheteroaryl and adamantyl; R¹⁴ is H or alkyl; R¹⁵ is H, C₁-C₂₀ alkyl, C₁-C₆ cycloalkyl, aryl or heteroaryl; and R¹⁷ is H, C₁-C₆ alkyl, aryl or heteroaryl; useful for treating cognitive disorders such as Alzheimer's disease are disclosed, as well as pharmaceutical compositions and methods of preparation. Also disclosed are combinations of compounds of formula (I) capable of enhancing ACh release with ACh'ase inhibitors.

734
332

-34-

What is Claimed:

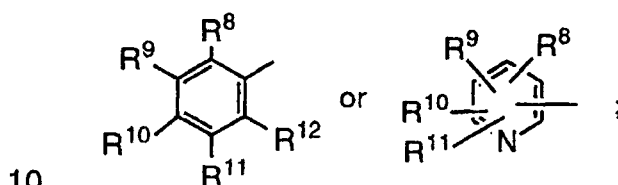
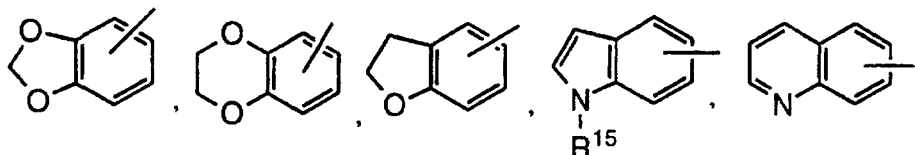
1. A compound having the structural formula



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein

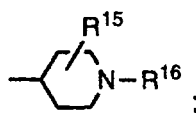
- 5 X is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -C(OR⁷)₂-, -CH₂-O-, -O-CH₂-, -CH=CH-, -CH₂-, -CH(C₁-C₆ alkyl)-, -C(C₁-C₆ alkyl)₂-, -CONR¹⁷-, -NR¹⁷CO-, -SO₂NR¹⁷- or -NR¹⁷SO₂-;

R is C₃-C₆ cycloalkyl,



R¹ is H, -CN, -CF₃, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, C₃-C₆ alkenyl, -COR¹⁵, -COO(C₁-C₆ alkyl), -COO(aryl), -COO(heteroaryl), -COO((C₁-C₆ alkyl)aryl), -COO((C₁-C₆ alkyl)heteroaryl), -(C₁-C₆ alkyl)aryl, -(C₁-C₆ alkyl)heteroaryl or -CON(R¹³)₂;

- 15 R² is C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, t-butoxycarbonyl or



R³ and R⁴ are independently selected from the group consisting of H, halo, -CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy and -OH;

- 20 R⁵ and R⁶ are independently selected from the group consisting of H, C₁-C₆ alkyl, -CF₃, C₁-C₆ alkoxy, -OH, C₁-C₆ alkylcarbonyl, C₁-C₆ alkoxycarbonyl, R¹³CONH-, R¹⁴OCONH-, R¹³NHCONH- and NH₂CONR¹³-;

7
340
333

-35-

R⁷ is independently selected from the group consisting of H and alkyl, provided that both R⁷ groups are not H; or the two R⁷ groups may be joined to form $-(CH_2)_p-$ wherein p is an integer of 2 to 4;

- R⁸, R⁹, R¹⁰, R¹¹ and R¹² are independently selected from the group consisting of H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, benzyloxy, benzyloxy substituted by -NO₂ or -N(R¹⁴), halo C₁-C₆ alkyl, polyhalo C₁-C₆ alkyl, -NO₂, -CN, -SO₂, -OH, -NH₂, -N(R¹⁴)₂, -HCO, polyhalo C₁-C₆ alkoxy, acyloxy, (C₁-C₄ alkyl)₃Si-, (C₁-C₆ alkyl)SO₀₋₂, arylsulfonyl, heteroaryl-sulfonyl, acyl, (C₁-C₆ alkoxy)CO-, -OCON(R¹⁴)₂, -NHCOO-(C₁-C₆)alkyl, -NHCO-(C₁-C₆ alkyl), phenyl, hydroxy(C₁-C₆ alkyl) or morpholino;

R¹³ is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -(C₁-C₆ alkyl)COOR¹⁵, aryl, heteroaryl, -(C₁-C₆ alkyl)aryl, -(C₁-C₆ alkyl)heteroaryl and adamantyl;

- R¹⁴ is independently selected from the group consisting of H and C₁-C₆ alkyl;

R¹⁵ is H, C₁-C₂₀ alkyl, C₁-C₆ cycloalkyl, aryl or heteroaryl;

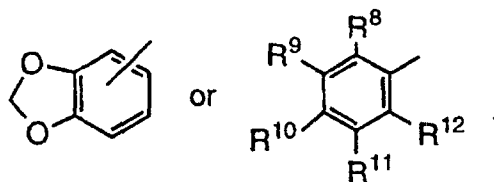
R¹⁶ is H, C₁-C₆ alkyl, -COR¹⁵, C₁-C₆ alkoxycarbonyl, (R¹⁴)₂NCO- or -SO₁₋₂-R¹⁵; and

R¹⁷ is H, C₁-C₆ alkyl, aryl or heteroaryl.

20

2. A compound of claim 1 wherein X is -SO- or -SO₂-.

3. A compound of any of claims 1 or 2 wherein R is



25

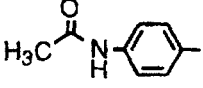
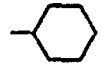
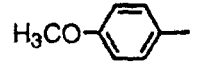
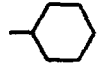
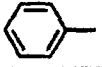
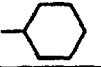
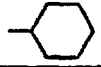
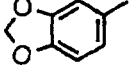
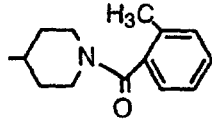
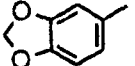
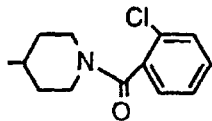
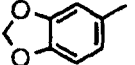
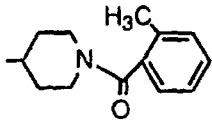
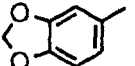
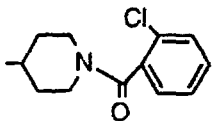
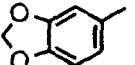
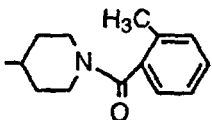
4. A compound of any of claims 1, 2 or 3 wherein R³ and R⁴ are each hydrogen and R⁵ and R⁶ are independently hydrogen or methyl.

5. A compound of any of claims 1, 2, 3 or 4 wherein R¹ is cyano, C₁-C₆ alkyl or C₃-C₆ alkenyl.

30

6. A compound of any of claims 1, 2, 3, 4 or 5 wherein R² is cyclohexyl



	-SO-	-CN		H
	-SO ₂ -	-CN		H
	-O-			-CH ₃
	-CH ₂ -	-CN		H
	-CH ₂ -	-CN		H
	-SO ₂ -	-CN		H
	-SO ₂ -	-CN		H
	-CH ₂ -	-CH ₃ -		H

8. A pharmaceutical composition comprising a compound as defined in any of claims 1, 2, 3, 4, 5, 6 or 7, alone or in combination with an acetylcholinesterase inhibitor, in combination with a pharmaceutically acceptable carrier.

5

9. A process for the preparation of a pharmaceutical composition as defined in claim 8 comprising admixing a compound as claimed in any of claims 1 to 7, alone or in combination with an acetylcholinesterase inhibitor, with a pharmaceutically acceptable carrier.

10

10. The use of a compound of any of claims 1 to 7, alone or in combination with an acetylcholinesterase inhibitor, for the preparation of a medicament for treating a cognitive or neurodegenerative disease.

15

11. A kit for treating a cognitive or neurodegenerative disease comprising separate containers in a single package that contain pharmaceutical compounds for use in combination, wherein one container contains a compound in accordance with any of claims 1 to 7 that

342
335

-38-

enhances acetylcholine release and a separate container contains an acetylcholinesterase inhibitor, said compound and inhibitor each being in a pharmaceutically acceptable carrier and their combined quantities being an effective amount.

- 5 12. A method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a compound of any of claims 1 to 7, alone or in combination with an acetylcholinesterase inhibitor.

10