

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-8794

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **532**

DE FECHA **30 DE SEPTIEMBRE DE 2003** EL TERMINO HABIL SEÑALADO

POR LA LEY EXPIRA EL **30 DE DICIEMBRE DEL 2003**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ☒ _____

Bogotá D.C, SEPTIEMBRE DE 2007

TABLA 13.7. Tipos de compuestos que se pueden obtener de los ácidos carboxílicos

Reacción	Producto	Sección
Cloruros de ácido:		
$\text{RCCl} + \text{H}_2\text{O} \longrightarrow \text{RCO}_2\text{H}$	ácido carboxílico	13.3C
$\text{RCCl} + \text{R}'\text{OH} \longrightarrow \text{RCO}_2\text{R}'$	éster	13.3C
$\text{RCCl} + \text{R}'_2\text{NH} \longrightarrow \text{RCNR}'_2$	amida	13.3C
$\text{RCCl} + \text{R}'\text{CO}_2^- \longrightarrow \text{RCOCR}'$	anhídrido	13.3C
$\text{RCCl} + \text{C}_6\text{H}_6 \xrightarrow{\text{AlCl}_3} \text{RCC}_6\text{H}_5$	aril cetona	10.9E, 13.3C
$\text{RCCl} \xrightarrow[\text{(2) H}_2\text{O, H}^+]{\text{(1) 2R}'\text{MgX}} \text{R}'_2\text{CH-CH}_2\text{R}$	alcohol 3°	13.3C
$\text{RCCl} + \text{R}'_2\text{Cd} \text{ o } \text{LiCuR}'_2 \longrightarrow \text{R}'_2\text{CH-CH}_2\text{R}$	cetona	13.3C
$\text{RCCl} \xrightarrow[\text{(2) H}_2\text{O}]{\text{(1) LiAlH}(\text{OR})_3} \text{RCH}_2\text{R}$	aldehído	13.3C
$\text{RCH}_2\text{CCl} + \text{Cl}_2 \longrightarrow \text{RCHClCCl}_2$	cloruro de α -cloroácido	13.3C
Anhídridos de ácido:		
$\text{RCOCR} + \text{H}_2\text{O} \longrightarrow 2 \text{RCO}_2\text{H}$	ácido carboxílico	13.4C
$(\text{RCO})_2\text{O} + \text{R}'\text{OH} \longrightarrow \text{RCO}_2\text{R}'$	éster	13.4C
$(\text{RCO})_2\text{O} + \text{R}'_2\text{NH} \longrightarrow \text{RCNR}'_2$	amida	13.4C
Ésteres:		
$\text{RCO}_2\text{R}' + \text{H}_2\text{O} \xrightarrow{\text{H}^+ \text{ o } \text{OH}^-} \text{RCO}_2\text{H}$	ácido carboxílico	13.5C
$\text{RCO}_2\text{R}' + \text{R}''\text{OH} \xrightarrow{\text{H}^+ \text{ o } \text{OR}''} \text{RCO}_2\text{R}''$	éster	13.5C
$\text{RCO}_2\text{R}' + \text{NH}_3 \longrightarrow \text{RC(=O)NH}_2$	amida	13.5C

(continúa)

TABLA 13.7.

Reacción	Producto	Sección
$\text{RCO}_2\text{R}' + [\text{H}] \longrightarrow \text{RCH}_2\text{OH} + \text{HOR}'$	alcoholes	13.5C
$\text{RCO}_2\text{R}' \xrightarrow{(1) 2 \text{ R}'\text{MgX}} \text{RCH}_2\text{OH} \xrightarrow{(2) \text{ H}_2\text{O}, \text{H}^+} \text{RCR}'_2$	alcohol 3 ^o	13.5C
Amidas:		
$\text{RCNR}'_2 + \text{H}_2\text{O} \xrightarrow{\text{H}^+ \text{ o } \text{OH}^-} \text{RCO}_2\text{H} + \text{HNR}'_2$	ácido carboxílico y amina	13.9C
$\text{RCNR}'_2 + [\text{H}] \longrightarrow \text{RCH}_2\text{NR}'_2$	amina	15.5C
$\text{RCNH}_2 + \text{Br}_2 + \text{OH}^- \longrightarrow \text{RNH}_2$	amina	15.5C
Nitrilos:		
$\text{RCN} + \text{H}_2\text{O} \xrightarrow{\text{H}^+ \text{ o } \text{OH}^-} \text{RCO}_2\text{H}$	ácido carboxílico	13.12D
$\text{RCN} + [\text{H}] \longrightarrow \text{RCH}_2\text{NH}_2$	amina	13.12D

*Los cloruros de ácido, ésteres y nitrilos se pueden emplear para sintetizar compuestos más complejos. Algunas de estas reacciones se explicarán en el Capítulo 14.

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 265/32, 279/12, 413/06, 413/04, 413/14	A1	(11) International Publication Number: WO 95/16679 (43) International Publication Date: 22 June 1995 (22.06.95)
(21) International Application Number: PCT/US94/14497 (22) International Filing Date: 13 December 1994 (13.12.94) (30) Priority Data: 169,889 17 December 1993 (17.12.93) US (60) Parent Application or Grant (63) Related by Continuation US 169,889 (CIP) Filed on 17 December 1993 (17.12.93) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DORN, Conrad, P. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). FINKE, Paul, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HALE, Jeffrey, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MacCOSS, Malcolm [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MILLS, Sander, G. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SHAH, Shrenik,		K. [IN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). CHAMBERS, Mark, Stuart [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). HARRISON, Timothy [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). LADDUWA-HETTY, Tamara [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). WILLIAMS, Brian, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, 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), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i>
(54) Title: MORPHOLINE AND THIOMORPHOLINE TACHYKININ RECEPTOR ANTAGONISTS		
(I)		
(57) Abstract Substituted heterocycles of general structural formula (I) or a pharmaceutically acceptable salt thereof, wherein: R¹ is selected from the group consisting of: hydrogen; C₁₋₆ alkyl, unsubstituted or substituted; C₂₋₆ alkenyl, unsubstituted or substituted; C₂₋₆ alkynyl; phenyl, unsubstituted or substituted; X is selected from the group consisting of: -O-, -S-, -SO-, -SO₂-; Y is selected from the group consisting of: a single bond, -O-, -S-, -CO-, -CH₂-, -CHR₅- and -CR¹⁵R¹⁶; Z = C₁₋₆ alkyl, are tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma and emesis, and calcium channel blockers useful in the treatment of cardiovascular conditions such as angina, hypertension or ischemia.		

- 243 -

R² and R³ are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁-6 alkyl, unsubstituted or substituted with one or more
of the substituents selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) C₁-6 alkoxy,
 - (d) phenyl-C₁-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - (h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (i) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined
above,
 - (j) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined
above,
 - (k) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined
above,
 - (l) -COR⁹, wherein R⁹ is as defined above, and
 - (m) -CO₂R⁹, wherein R⁹ is as defined above;
- (3) C₂-6 alkenyl, unsubstituted or substituted with one or more
of the substituent(s) selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) C₁-6 alkoxy,
 - (d) phenyl-C₁-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - (h) -CONR⁹R¹⁰ wherein R⁹ and R¹⁰ are as defined
above,
 - (i) -COR⁹ wherein R⁹ is as defined above,
 - (j) -CO₂R⁹, wherein R⁹ is as defined above;

- 244 -

- (4) C₂-6 alkynyl;
- (5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
 - (b) C₁-6 alkoxy,
 - (c) C₁-6 alkyl,
 - (d) C₂-5 alkenyl,
 - (e) halo,
 - (f) -CN,
 - (g) -NO₂,
 - (h) -CF₃,
 - (i) -(CH₂)_m-NR⁹R¹⁰, wherein m, R⁹ and R¹⁰ are as defined above,
 - (j) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (k) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (l) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (m) -CO₂NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (n) -COR⁹, wherein R⁹ is as defined above;
 - (o) -CO₂R⁹, wherein R⁹ is as defined above;
- and the groups R¹ and R² may be joined together to form a heterocyclic ring selected from the group consisting of:
- (a) pyrrolidinyl,
 - (b) piperidinyl,
 - (c) pyrrolyl,
 - (d) pyridinyl,
 - (e) imidazolyl,
 - (f) oxazolyl, and
 - (g) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or

- 246 -

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

- (i) C₁-6alkyl,
- (ii) oxo,
- (iii) C₁-6alkoxy,
- (iv) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
- (v) halo, and
- (vi) trifluoromethyl;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of:

- (1) hydrogen;
- (2) C₁-6 alkyl, unsubstituted or substituted with one or more of the substituents selected from:
 - (a) hydroxy,
 - (b) oxo,
 - (c) C₁-6 alkoxy,
 - (d) phenyl-C₁-3 alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - (g) halo,
 - (h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (i) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (j) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (k) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 - (l) -COR⁹, wherein R⁹ is as defined above, and
 - (m) -CO₂R⁹, wherein R⁹ is as defined above;
- (3) C₂-6 alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
 - (a) hydroxy,
 - (b) oxo,