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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES
Folios: 2

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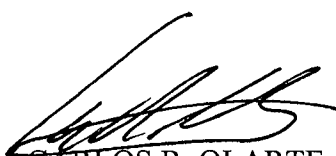
“DERIVADOS DE 1-TRIFLUOROMETIL-4-HIDROXI-7-
PIPERIDINIL-AMINOMETILCROMANO”.

Solicitante: **PFIZER PRODUCTS INC.**

**SOLICITUD DE EXAMEN DE FONDO SEGÚN EL ARTICULO 44 DE LA
DECISION 486, GACETA No. 517**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina de Naciones, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Adjunto recibo por el monto de \$ 318.000 pesos para cubrir la tasa correspondiente, según la Resolución 44691 del año 2001.

Atentamente,



CARLOS R. OLARTE
C.C. No. 79'782.747 de Bogotá
T.P. 74.295

Anexos: Recibo por \$ 318.000 pesos
RCC/P2000-000068 160702.DOC

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2
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Radicacion : 62333397 62368882

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Fecha (AMD): 2002-07-17 17:15:21

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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RECIBO OFICIAL DE CAJA : 02 - 41,108
FECHA : JUNIO 24 DE 2002

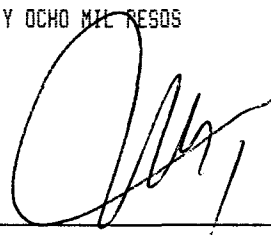
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	4317419	24/06/2002	39,418,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
		TOTAL :	\$ 318,000.00

SON: RESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : 

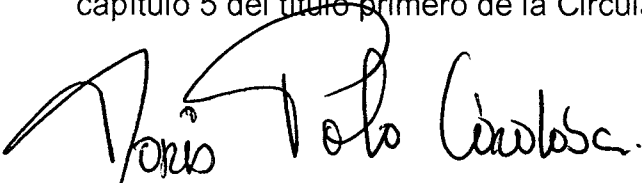
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	EP 0826684	1-6	Nivel Inventivo
2	WO 9708144	1-6	Nivel Inventivo

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.

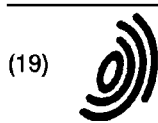
Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única Nº 10 de 2001



Doris Polo C.
Jefe de la División de Nuevas Creaciones (e)

El anterior requerimiento fue notificado por fijación en lista, de fecha 12 MAYO 2005

CONCEPTO TÉCNICO Número 0594	EXAMINADOR TÉCNICO Código 202024
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(12)

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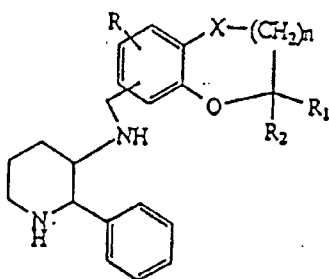
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(54) PIPERIDINE DERIVATIVES

(57) Piperidine derivatives represented by general formula (I)



or pharmaceutically acceptable acid addition salts thereof:

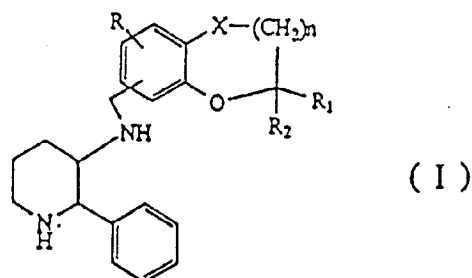
wherein n represents an integer of 0 or 1; X represents CH₂, O or CH-CH₃; R represents hydrogen, halogen, lower alkyl, hydroxy, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, substituted aminosulfonyl or nitro; R₁ and R₂ may be the same or different and each represents hydrogen or lower alkyl, are disclosed. The piperidine derivatives have an antagonism on Substance P and is useful as a preventive or remedy for asthma, vomiting, etc.

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derivatives of the present invention, therefore, are expected to be used as a preventive or remedy for a variety of diseases mediated by Substance P and are useful for pharmaceutical industries.

Claims

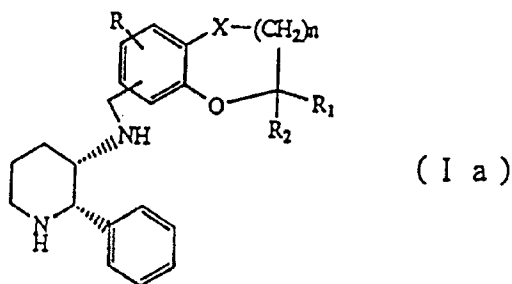
1. Piperidine derivatives represented by general formula (I)



or pharmaceutically acceptable acid addition salts thereof:

wherein n represents an integer of 0 or 1; X represents CH₂, O or CH-CH₃; R represents hydrogen, halogen, lower alkyl, hydroxy, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, substituted aminosulfonyl or nitro; R₁ and R₂ may be the same or different and each represents hydrogen or lower alkyl.

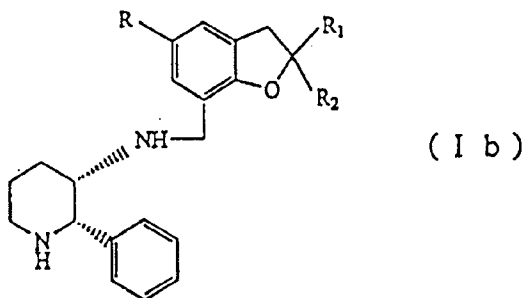
2. Cis-piperidine derivatives represented by general formula (Ia)



or pharmaceutically acceptable acid addition salts thereof:

wherein n represents an integer of 0 or 1; X represents CH₂, O or CH-CH₃; R represents hydrogen, halogen, lower alkyl, hydroxy, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, substituted aminosulfonyl or nitro; R₁ and R₂ may be the same or different and each represents hydrogen or lower alkyl.

3. Cis-piperidine derivatives represented by general formula (Ib)



or pharmaceutically acceptable acid addition salts thereof:

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wherein R represents hydrogen, halogen, lower alkyl, hydroxy, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, substituted aminosulfonyl or nitro: R₁ and R₂ may be the same or different and each represents hydrogen or lower alkyl.

- 5 4. Piperidine derivatives or pharmaceutically acceptable acid addition salts thereof as claimed in any of Claims 1 to 3, which have an antagonism on Substance P.
5. A pharmaceutical composition which comprises an effective amount of the piperidine derivative or pharmaceutically acceptable acid addition salt thereof as claimed in Claims 1 to 3, and a pharmaceutically acceptable carrier.
- 10 6. A preventive or remedy for asthma which comprises the piperidine derivative or pharmaceutically acceptable acid addition salt thereof as claimed in any of Claims 1 to 3 as an effective component.
7. A preventive or remedy for vomiting which comprises the piperidine derivative or pharmaceutically acceptable acid addition salt thereof as claimed in any of Claims 1 to 3 as an effective component.
- 15 8. A formulation for oral administration, parenteral administration, intrarectal administration or percutaneous administration, which comprises the piperidine derivative or pharmaceutically acceptable acid addition salt as claimed in Claims 1 to 3 as an effective component.

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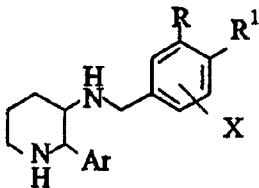
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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

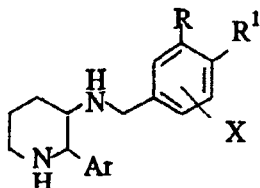
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 211/56, A61K 31/445	A1	(11) International Publication Number: WO 97/08144 (43) International Publication Date: 6 March 1997 (06.03.97)
(21) International Application Number: PCT/IB96/00572 (22) International Filing Date: 10 June 1996 (10.06.96) (30) Priority Data: PCT/IB95/00683 24 August 1995 (24.08.95) WO <i>(34) Countries for which the regional or international application was filed:</i> JP et al. (71) Applicant (for JP only): PFIZER PHARMACEUTICALS INC. [JP/JP]; Mitsui Building, 1-1, Nishi-shinjuku 2-chome, Shinjuku-ku, Tokyo 163 (JP). (71) Applicant (for all designated States except JP US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): SATAKE, Kunio [JP/JP]; 4-58, Hakusan-cho, Handa-shi, Aichi-ken 475 (JP). SHISHIDO, Yuji [JP/JP]; 362, Aza-Giro, Oaza-Okuda, Mihama-cho, Chita-gun, Aichi-ken 470-32 (JP). WAKABAYASHI, Hiroaki [JP/JP]; 3-1, Sumiyoshi-cho, Kariya-shi, Aichi-ken 448 (JP).		(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US). (81) Designated States: AU, BG, BR, BY, CA, CN, CZ, HU, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN, 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: SUBSTITUTED BENZYLAMINOPIPERIDINE COMPOUNDS  (I) (57) Abstract This invention provides a compound of formula (I) and its pharmaceutically acceptable salts, wherein R is halo C₁-C₈ alkyl, halo C₂-C₈ alkenyl, halo C₂-C₈ alkynyl or halo C₁-C₈ alkyl substituted by hydroxy or C₁-C₈ alkoxy; R¹ is hydrogen, halo or C₁-C₆ alkoxy; or R and R¹, together with the two carbon atoms shared between the benzene ring and the R and R¹, complete a fused C₄-C₆ cycloalkyl wherein one carbon atom is optionally replaced by oxygen and wherein one or two of the carbon atoms are optionally substituted by up to five substituents selected from halo, C₁-C₆ alkyl and halo C₁-C₆ alkyl; X is C₁-C₆ alkoxy, halo C₁-C₆ alkoxy, phenoxy or halo; and Ar is phenyl optionally substituted by halo. These compounds are of use in treating a gastrointestinal disorder, a central nervous system (CNS) disorder, an inflammatory disease, emesis, urinary incontinence, pain, migraine, sunburn, diseases, disorders and adverse conditions caused by <i>Helicobacter pylori</i>, or angiogenesis especially CNS disorders in a mammalian subject, especially humans.		

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211CLAIMS

1. A compound of the formula (I):



(I)

and its pharmaceutically acceptable salts, wherein

5 R is halo C₁-C₈ alkyl, halo C₂-C₈ alkenyl, halo C₂-C₈ alkynyl or halo C₁-C₈ alkyl substituted by hydroxy or C₁-C₈ alkoxy; R¹ is hydrogen, halo or C₁-C₆ alkoxy; or

R and R¹, together with the two carbon atoms shared between the benzene ring and the R and R¹, complete a fused C₄-C₆ cycloalkyl wherein one carbon atom is optionally replaced by oxygen and wherein one or two of the carbon atoms are
10 optionally substituted by up to five substituents selected from halo, C₁-C₆ alkyl and halo C₁-C₆ alkyl;

X is C₁-C₆ alkoxy, halo C₁-C₆ alkoxy, phenoxy or halo; and

Ar is phenyl optionally substituted by halo.

2. A compound according to claim 1, wherein X is halo, methoxy, difluoromethoxy, trifluoromethoxy or phenoxy, and is at 2-position on the phenyl ring;
15 and Ar is phenyl.

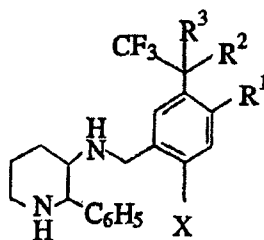
3. A compound according to claim 2, wherein X is methoxy, difluoromethoxy or trifluoromethoxy.

4. A compound according to claim 2 or 3, wherein R is C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, these groups being substituted by two to
20 seven halogen atoms; and R¹ is hydrogen or methoxy.

5. A compound according to claim 2 or 3, wherein R and R¹, together with the two carbon atoms shared between the benzene ring and the R and R¹, complete a fused C₄-C₆ cycloalkyl wherein one carbon atom is optionally replaced by oxygen and
25 wherein one or two of the carbon atoms are optionally substituted by up to four substituents selected from a fluorine atom and trifluoromethyl.

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6. A compound according to claim 1, which is represented by the general formula (Ia):



(Ia)

wherein R¹ is hydrogen, halo or methoxy; and R² and R³ is independently
5 selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl and C₂-C₆ alkynyl, or R² and R³ together
complete C₂-C₆ alkylidene, wherein the alkyl, alkenyl, alkynyl and alkylidene moiety
are optionally substituted by up to seven halogen atoms;

or R¹ and R² are taken together to complete a fused C₄-C₆ cycloalkyl wherein one
carbon atom is optionally replaced by oxygen, the C₄-C₆ cycloalkyl being optionally
10 substituted by up to four substituents selected from halo, C₁-C₄ alkyl, and halo C₁-C₄
alkyl.

7. A compound according to claim 4, wherein R is C₁-C₆ alkyl, hydroxy C₁-C₆
alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, these groups being substituted by two to three
fluorine atoms.

15 8. A compound according to claim 7, wherein R is C₁-C₆ alkyl substituted by
two to three fluorine atoms.

9. A compound according to claim 4, wherein R is C₁-C₆ alkyl, hydroxy C₁-C₆
alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, these groups being substituted by four to seven
fluorine atoms.

20 10. A compound according to claim 7, wherein R is trifluoromethyl,
difluoroethyl, trifluoroethyl, trifluoroisopropyl, trifluoro-*tert*-butyl, trifluoro-1,1-
dimethylmethyl-3-butynyl or 2-chlorotrifluoroisopropyl.

11. A compound according to claim 9, wherein R is pentafluoroethyl,
pentafluoropropyl, pentafluoroisopropenyl, hexafluoroisopropyl, heptafluoroisopropyl,
25 hexafluoro-2-hydroxyisopropyl or hexafluoro-*tert*-butyl.

12. A compound according to claim 5, wherein R and R¹ together with the two

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carbon atoms shared between the benzene ring and the R and R', complete trifluorocyclopentyl, trifluoromethylcyclohexyl, difluorocyclohexyl or difluorodimethylcyclohexyl.

13. A compound according to claim 7 selected from

5 (2*S*, 3*S*)-3-(2-Fluoro-5-(trifluoromethyl)benzyl)amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-(2-Chloro-5-(trifluoromethyl)benzyl)amino-2-phenylpiperidine or its salts;

10 (2*S*, 3*S*)-3-(2-Methoxy-5-(trifluoromethyl)benzyl)amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-(2-Phenoxy-5-(trifluoromethyl)benzyl)amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-(5-(1,1-Difluoroethyl)-2-(trifluoromethoxy)benzyl)amino-2-phenylpiperidine or its salts;

15 (2*S*, 3*S*)-3-(5-(1,1-Difluoroethyl)-2-methoxybenzyl)amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-(2-Methoxy-5-(2,2,2-trifluoroethyl)benzyl)amino-2-phenylpiperidine or its salts;

20 (2*S*, 3*S*)-3-(2-Methoxy-5-(1-(trifluoromethyl)ethyl)benzyl)amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-[5-(1,1-Dimethyl-4,4,4-trifluoro-2-butynyl)-2-methoxybenzyl] amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-[5-(1,1-Dimethyl-2,2,2-trifluoroethyl)-2-methoxybenzylamino]-2-phenylpiperidine or its salt;

25 (2*S*, 3*S*)-3-(2,4-Dimethoxy-5-(2,2,2-trifluoroethyl)benzyl)amino-2-phenylpiperidine or its salts; and

(2*S*, 3*S*)-3-[5-[(1-Chloro-1-(trifluoromethyl)ethyl)-2-methoxybenzylamino]-2-phenylpiperidine or its salts.

14. A compound according to claim 9 selected from

30 (2*S*, 3*S*)-2-Phenyl-3-(5-(2,2,2-trifluoro-1-(trifluoromethyl)ethyl)-2-

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methoxybenzyl)aminopiperidine or its salts;

(2*S*, 3*S*)-2-Phenyl-3-(5-(1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl)-2-methoxybenzyl)aminopiperidine or its salts;

(2*S*, 3*S*)-3-(2-Methoxy-5-(1,1,2,2,2-pentafluoroethyl)benzyl)amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-2-Phenyl-3-(5-(2,2,2-trifluoro-1-methyl-1-(trifluoromethyl)ethyl)-2-methoxybenzyl)aminopiperidine or its salts;

(2*S*,3*S*)-3-[5-[2,2-Difluoro-1-(trifluoromethyl)ethenyl]-2-methoxybenzyl]amino-2-phenylpiperidine or its salts; and

(2*S*, 3*S*)-3-(2-Methoxy-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)benzyl)amino-2-phenylpiperidine or its salts.

15. A compound according to claim 12 selected from

(2*S*, 3*S*)-3-[5-Methoxy-1-(trifluoromethyl)indan-6-yl)methylamino]-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-((6-Methoxy-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-7-yl)methyl)amino-2-phenylpiperidine or its salts; and

(2*S*, 3*S*)-3-((2,2-Difluoro-6-methoxy-1,2,3,4-tetrahydronaphthalen-7-yl)methyl)amino-2-phenylpiperidine or its salts.

16. A compound according to claim 10 selected from

(2*S*, 3*S*)-3-(2-Methoxy-5-(trifluoromethyl)benzyl)amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-(2-Methoxy-5-(2,2,2-trifluoroethyl)benzyl)amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-(2-Methoxy-5-(1-(trifluoromethyl)ethyl)benzyl)amino-2-phenylpiperidine or its salts;

(2*S*, 3*S*)-3-(5-(1,1-Difluoroethyl)-2-(trifluoromethoxy)benzyl)amino-2-phenylpiperidine or its salts, and

(2*S*, 3*S*)-3-[5-(1,1-Dimethyl-2,2,2-trifluoroethyl)-2-methoxybenzylamino]-2-phenylpiperidine or its salts.

17. A compound according to claim 12 (2*S*, 3*S*)-2-Phenyl-3-(5-(2,2,2-trifluoro-1-

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(trifluoromethyl)ethyl)-2-methoxybenzyl)aminopiperidine or its salt.

18. A compound according to claim 15 (2S, 3S)-3-[5-Methoxy-1-trifluoromethylindan-6-yl)methylamino]-2-phenylpiperidine or its salts.

19. A method of treating or preventing a gastrointestinal disorder, a central
5 nervous system disorder, an inflammatory disease, emesis, urinary incontinence, pain, migraine, sunburn, a diseases, disorders and adverse conditions caused by *Helicobacter pylori*, or angiogenesis in a mammalian subject which comprises administering to the said subject a therapeutically effective amount of a compound of claim 1.

20. A pharmaceutical composition for treating or preventing a gastrointestinal
10 disorder, a central nervous system disorder, an inflammatory disease, emesis, urinary incontinence, pain, migraine, sunburn, a diseases, disorders and adverse conditions caused by *Helicobacter pylori*, or angiogenesis in a mammalian subject which comprises a therapeutically effective amount of a compound of claim 1 together with a pharmaceutically acceptable carrier.