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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

168
169
No. 07-088652-00003-0000
FOLIO 11 PATENTE DE INVENCION
A 1538 PLICION
Folios 2

Trámite : 011
Evento : 378
Actuación : 538

Referencia : Expediente No. 07.088.652
Asunto : Solicitud de Patente para **DERIVADOS DE PIRIDINA SUSTITUIDOS**
Solicitante : **H. LUNDBECK A/S**
Clase : A61K 031/5377, A61P 025/000, C07D 413/004
Publicada en : La Gaceta No. 592 Del 30 de mayo de 2008
Fecha de Solicitud : 29 de agosto de 2007

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$420.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44372 de 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,



EMILIO FERRERO
T.P.A. No. 31.929

COLO-03003-841-067-3
ASG\SCT\ID-138848\WPCL3003
No. M-2008-138848\ASG

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 86,882
FECHA : NOVIEMBRE 4 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-088652- -00003-0000

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No. 11 PATENTILYII Lva 378 FASLNACIONALI
Act 538 PLICION Folios 2

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	05283	07/11/2008	50,330,000.00

***** CONCEPT *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
TOTAL :			\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

0010:03003-841-067-3

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-88652

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **592** DE

FECHA **30 DE MAYO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **28 DE AGOSTO DE 2008**

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 X

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(2)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

202012

Bogotá, D.C., 25 de enero de 2011

Apoderado: Emilio Ferrero

ASUNTO	Radicación	07-88652
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	Nº 0 2330

Patente de Invención ☒

Vía PCT fase nacional ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/DK2006/000123

Fecha de Presentación Internal. 02/mar/2006

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

1. Documentos estudiados

1.1. Descripción: Folios: 72 a 139 como se radicó inicialmente

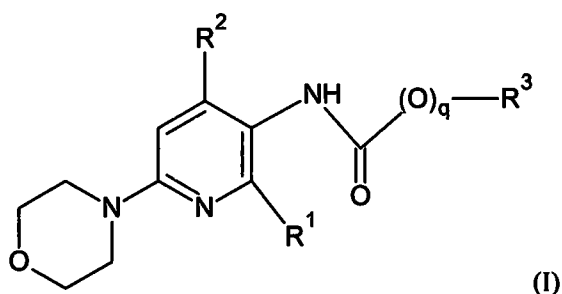
1.2. Reivindicaciones: Folios 140 a 147 Como se radicó inicialmente

1.3 Prioridad: Folio 1: DK PA200500321, 03/mar/2005

1. Objeto de la invención

Título de la solicitud: DERIVADOS DE PIRIDINA SUSTITUIDOS.

El objeto de la invención son los derivados de N-[2,4-disustituido-6-(morfolin-4-il)piridin-3-il]carboxamida-sustituida y derivados de sustituido-[2,4-disustituido-6-(morfolin-4-il)piridin-3-il]carbamato cubiertos bajo la fórmula Markush (I):



- Reivindicaciones 1–11: Un compuesto de la fórmula (I).
- Reivindicación 12: Composiciones que los contienen.
- Reivindicación 13-21: Reivindicaciones de uso.

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.): C07D413/04, A61K31/5377, A61P25/00.

2. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486 de la C.A.N.)

Las reivindicaciones 13-21 reclaman los usos y de acuerdo con la legislación actual vigente, el uso no se considera para protección, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina “... *Los Países Miembros otorgarán patentes para las invenciones sean de productos o procedimientos en todos los campos de la tecnología...*”; Aquí NO se hace alusión al uso como factor patentable; los segundos usos no son patentables por aplicación del Art. 21. Asimismo, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables.

3. Determinación del Estado de la Técnica

Considerando la fecha de prioridad reclamada de la presente solicitud de patente 11/nov/2004, se realizó la búsqueda del estado de la técnica, en bases de datos donde ésta oficina tiene acceso libre, para búsquedas de documentos relacionados con la materia que se reclama como nueva e inventiva en la presente solicitud.

Encontrándose los siguientes documentos relevantes:

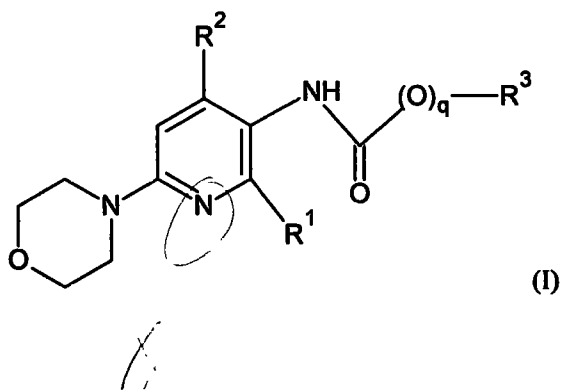
N°	Documento	Título	Fecha de Presentación*
D1	WO2005087754	Substituted morpholine and thiomorpholine derivatives.	12/mar/2004

*Se trata de una solicitud colombiana esta fecha corresponde también a la fecha de presentación de la solicitud colombiana aún sin haber sido publicada o sin haberse cumplido el plazo previsto en el art.40.

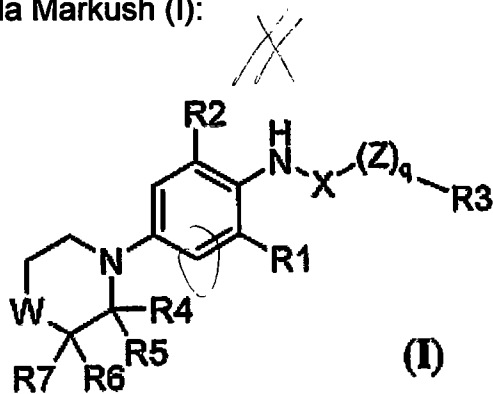
4. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

4.1. Novedad (artículo 16 D486 de la C.A.N.)

La solicitud en estudio reclama los derivados de N-[2,4-disustituido-6-(morfolin-4-il)piridin-3-il]carboxamida-sustituida y derivados de sustituido-[2,4-disustituido-6-(morfolin-4-il)piridin-3-il]carbamato cubiertos bajo la fórmula Markush (I):



La anterioridad D1 [WO2005087754] describe derivados de N-[2,4-disustituido-6-(morfolin/tiomorfolin-4-il)piridin-3-il]carboxamida-sustituida y derivados de sustituido-[2,4-disustituido-6-(morfolin/tiomorfolin-4-il)piridin-3-il]carbamato cubiertos bajo la fórmula Markush (I):



wherein

q is 0 or 1;

W is O or S;

X is CO;

Z is O;

R1 is selected from the group consisting of halogen, cyano, C₁₋₆-alk(en/yn)yl,

C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl,

halo-C₃₋₈-cycloalk(en)yl, halo-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl,

C₁₋₆-alk(en/yn)yloxy, C₃₋₈-cycloalk(en)yloxy and C₃₋₈-cycloalk(en)yl-

C₁₋₆-alk(en/yn)yloxy;

R2 is selected from the group consisting of halogen, cyano, C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl, halo-C₃₋₈-cycloalk(en)yl, halo-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yloxy, C₃₋₈-cycloalk(en)yloxy, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yloxy, optionally substituted phenyl and optionally substituted pyridyl; wherein phenyl and pyridyl are optionally substituted with one or more substituents independently being halogen, C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl or C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl;

R3 is selected from the group consisting of C₁₋₁₀-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, Ar-C₁₋₆-alk(en/yn)yl, Ar-C₃₋₈-cycloalk(en)yl, Ar-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl and Ar; and

each of R4, R5, R6 and R7 is independently selected from the group consisting of hydrogen and Ar;

as the free base or salts thereof.
Véase todo el documento D1.

Tal como puede verse la materia reclamada como nueva está comprendida en la anterioridad citada D1, por lo tanto se considera que la presente solicitud no cumple con el requisito exigido en artículo 16 D486 de la C.A.N.

5. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO2005087754	1-21	Novedad

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

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de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (e)

El anterior requerimiento fue notificado por fijación en lista, de fecha
_____, 1 FEB. 2011.

CONCEPTO TECNICO No. 345	EXAMINADOR TECNICO Cód N°202012
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(19) World Intellectual Property
Organization
International Bureau



PCT

(43) International Publication Date
22 September 2005 (22.09.2005)

(10) International Publication Number
WO 2005/087754 A1

(51) International Patent Classification⁷: C07D 295/12,
265/06, 279/12, 417/04, A61K 31/4406, 31/541, 31/5355,
A61P 25/22

(DK). WATSON, William Patrick [GB/DK]; Jyllingevej
81 st., DK-2720 Vanløse (DK).

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PCT/DK2005/000159

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(25) Filing Language: English

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PA 200400412 12 March 2004 (12.03.2004) DK
60/552,574 12 March 2004 (12.03.2004) US

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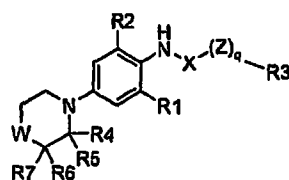
(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
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GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED MORPHOLINE AND THIOMORPHOLINE DERIVATIVES



(I)

(57) Abstract: The present invention relates to morpholine
and thiomorpholine derivatives of the general formula I or
pharmaceutically acceptable salts thereof and their use.

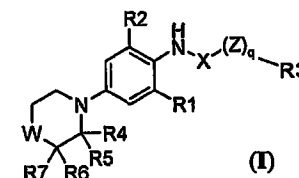
The invention furthermore concerns the use of a compound of formula I in a method
of treatment of seizure disorders, anxiety disorders, neuropathic pain and migraine
pain disorders or neurodegenerative disorders.

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Detailed description of the invention

The present invention relates to substituted morpholine and thiomorpholine
derivatives which are potent openers of KCNQ potassium channels.

10 Accordingly, the present invention relates to substituted morpholine and
thiomorpholine derivatives of the general formula I



(I)

wherein

q is 0 or 1;

15 W is O or S;

X is CO;

Z is O;

R1 is selected from the group consisting of halogen, cyano, C₁₋₆-alk(en/yn)yl,

20 C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl,
halo-C₃₋₈-cycloalk(en)yl, halo-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl,
C₁₋₆-alk(en/yn)yloxy, C₃₋₈-cycloalk(en)yloxy and C₃₋₈-cycloalk(en)yl-
C₁₋₆-alk(en/yn)yloxy;

25 R2 is selected from the group consisting of halogen, cyano, C₁₋₆-alk(en/yn)yl,
C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl,
halo-C₃₋₈-cycloalk(en)yl, halo-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl,
C₁₋₆-alk(en/yn)yloxy, C₃₋₈-cycloalk(en)yloxy, C₃₋₈-cycloalk(en)yl-

30 C₁₋₆-alk(en/yn)yloxy, optionally substituted phenyl and optionally substituted pyridyl;
wherein phenyl and pyridyl are optionally substituted with one or more substituents

independently being halogen, C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl or C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl;

R3 is selected from the group consisting of C₁₋₁₀-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, Ar-C₁₋₆-alk(en/yn)yl, Ar-C₃₋₈-cycloalk(en)yl, Ar-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl and Ar; and

each of R4, R5, R6 and R7 is independently selected from the group consisting of hydrogen and Ar;

as the free base or salts thereof.

In one embodiment of the compound of formula I, q is 0;

in another embodiment of the compound of formula I, q is 1.

In a further embodiment of the compound of formula I, W is an oxygen atom; in another embodiment W is a sulphur atom.

In a further embodiment of the compound of formula I, R1 is selected from the group consisting of C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, halo-C₃₋₈-cycloalk(en)yl, halo-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl-oxo and C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl-oxo; in another embodiment R1 is selected from the group consisting of halogen, halo-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl and cyano.

Typically, R1 is selected from the group consisting of halogen, cyano, C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl and C₁₋₆-alk(en/yn)yl-oxo.

To further illustrate without limiting the invention an embodiment of R1 is halogen; another embodiment of R1 is cyano;

another embodiment of R1 is C₁₋₆-alk(en/yn)yl; another embodiment of R1 is halo-C₁₋₆-alk(en/yn)yl; another embodiment of R1 is C₁₋₆-alk(en/yn)yl-oxo.

In a further embodiment of the compound of formula I, R2 is selected from the group consisting of C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, halo-C₃₋₈-cycloalk(en)yl, halo-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl-oxo and C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl-oxo;

in another embodiment R2 is selected from the group consisting of halogen, halo-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl and cyano.

Typically, R2 is selected from the group consisting of halogen, cyano,

C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl-oxo, optionally substituted phenyl and optionally substituted pyridyl.

To further illustrate without limiting the invention an embodiment of R2 is halogen; another embodiment of R2 is cyano;

another embodiment of R2 is C₁₋₆-alk(en/yn)yl;

another embodiment of R2 is halo-C₁₋₆-alk(en/yn)yl;

another embodiment of R2 is C₁₋₆-alk(en/yn)yl-oxo;

another embodiment of R2 is optionally substituted phenyl;

another embodiment of R2 is optionally substituted pyridyl.

In a further embodiment of the compound of formula I, R2, optionally substituted phenyl and optionally substituted pyridyl may be substituted with one or more substituents

independently selected from the group consisting of halogen or C₁₋₆-alk(en/yn)yl;

in another embodiment of R2, phenyl and pyridyl are not substituted;

in yet another embodiment of R2, optionally substituted phenyl and optionally substituted pyridyl are substituted with one substituent;

in yet another embodiment of R2, optionally substituted phenyl and optionally

substituted pyridyl are substituted with two substituents;

in yet another embodiment of R2, optionally substituted phenyl and optionally substituted pyridyl are substituted with three substituents.

In a further embodiment of the compound of formula I, R3 is selected from the group consisting of C₃₋₈-cycloalk(en)yl, Ar-C₃₋₈-cycloalk(en)yl and Ar-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl.

Typically, R3 is selected from the group consisting of C₁₋₁₀-alk(en/yn)yl,

C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, Ar-C₁₋₆-alk(en/yn)yl and Ar

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One embodiment relates to compounds of general formula I wherein the stereo configuration on the carbon atom to which R4 and R5 are attached is the *S*-configuration.

Another embodiment relates to compounds of general formula I wherein the stereo configuration on the carbon atom to which R4 and R5 are attached is the

5 *R*-configuration.

Yet another embodiment relates to compounds of general formula I wherein the stereo configuration on the carbon atom to which R6 and R7 are attached is the *S*-configuration.

10 Yet another embodiment relates to compounds of general formula I wherein the stereo configuration on the carbon atom to which R6 and R7 are attached is the *R*-configuration.

Yet another embodiment relates to compounds of general formula I wherein the stereo configuration on the carbon atom to which R4 and R5 are attached is identical to the

15 stereo configuration on the carbon atom to which R6 and R7 are attached.

Yet another embodiment relates to compounds of general formula I wherein the stereo configuration on the carbon atom to which R4 and R5 are attached is different from the stereo configuration on the carbon atom to which R6 and R7 are attached.

20 The compounds of the following list and salts thereof exemplifies the invention, the list is in no way intended to be construed as limiting:

N-(2-Bromo-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-2-(4-fluoro-phenyl)-acetamide;

2-Cyclopentyl-*N*-(2-bromo-6-trifluoromethyl-4-morpholin-4-yl-phenyl)-acetamide;

25 *N*-(2-Bromo-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-3-cyclopentyl-propionamide;

N-(2-Chloro-6-cyano-4-morpholin-4-yl-phenyl)-3-cyclohexyl-propionamide;

2-Cyclopentyl-*N*-(2,6-dimethyl-4-thiomorpholin-4-yl-phenyl)-acetamide;

2-Cyclopentyl-*N*-[2,6-dimethyl-4-(2-phenyl-morpholin-4-yl)-phenyl]-acetamide;

30 2-Cyclopentyl-*N*-[2,6-dimethyl-4-(2-phenyl-thiomorpholin-4-yl)-phenyl]-acetamide;

2-Cyclopentyl-*N*-[2,6-dimethyl-4-(3-pyridin-3-yl-thiomorpholin-4-yl)-phenyl]-acetamide;

2-Cyclopentyl-*N*-(2,6-dimethyl-4-[2-(4-trifluoromethyl-phenyl)-thiomorpholin-4-yl]-phenyl)-acetamide;

N-(4-[2-(2-Chloro-phenyl)-thiomorpholin-4-yl]-2,6-dimethyl-phenyl)-2-cyclopentyl-acetamide;

2-Bicyclo[2.2.1]hept-2-yl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

2-Cyclohexyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

5 3-(3,4-Difluoro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-propionamide;

2-Cyclopentyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-carbamic acid butyl ester;

2-(4-Chloro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

2,3-Dihydro-benzofuran-2-carboxylic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-

10 amide;

3-Cyclohexyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-propionamide;

3-Cyclopentyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-propionamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-(4-fluoro-phenyl)-acetamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-thiophen-2-yl-acetamide;

15 *N*-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-3,3-dimethyl-butyramide;

Hexanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;

2-Cycloheptyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-carbamic acid benzyl ester;

(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-carbamic acid 2-chloro-benzyl ester;

20 3,5,5-Trimethyl-hexanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;

Octanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;

Heptanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-phenyl-acetamide;

2-(3,4-Dichloro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

25 2-(4-Allyloxy-3-chloro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-(3-trifluoromethyl-phenyl)-acetamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-naphthalen-2-yl-acetamide;

3-(3-Chloro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-propionamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-(3,4-dimethyl-phenyl)-acetamide;

30 2-(3-Bromo-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

2-(3-Chloro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-*p*-tolyl-acetamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-*m*-tolyl-acetamide;

2-(3,4-Difluoro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

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In the second part, the document addresses the challenges faced by organizations in implementing effective internal controls. It highlights the need for a strong culture of compliance and the importance of regular training and monitoring. The document also discusses the role of technology in enhancing the efficiency and accuracy of record-keeping processes.

The third part of the document provides a detailed overview of the various types of records that must be maintained, including financial statements, contracts, and correspondence. It also discusses the requirements for the storage and retention of these records, ensuring that they are accessible and secure for the long term.

Finally, the document concludes by emphasizing the ongoing nature of the record-keeping process. It stresses that organizations must continuously review and update their record-keeping practices to ensure they remain effective and compliant with the latest regulations and standards.

The second part of the document focuses on the importance of maintaining accurate records of all transactions. It emphasizes that proper record-keeping is essential for the integrity of the financial system and for the ability to detect and prevent fraud. The document also outlines the responsibilities of individuals involved in the process, including the need for transparency and accountability.

In the third part, the document addresses the challenges faced by organizations in implementing effective internal controls. It highlights the need for a strong culture of compliance and the importance of regular training and monitoring. The document also discusses the role of technology in enhancing the efficiency and accuracy of record-keeping processes.

The fourth part of the document provides a detailed overview of the various types of records that must be maintained, including financial statements, contracts, and correspondence. It also discusses the requirements for the storage and retention of these records, ensuring that they are accessible and secure for the long term.

Finally, the document concludes by emphasizing the ongoing nature of the record-keeping process. It stresses that organizations must continuously review and update their record-keeping practices to ensure they remain effective and compliant with the latest regulations and standards.

- N*-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-(3-fluoro-phenyl)-acetamide;
N-(2-Bromo-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-3-cyclohexyl-propionamide;
N-(2-Bromo-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-2-(3-fluoro-phenyl)-acetamide;
 5 *N*-(2-Bromo-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-propionamide;
N-(2-Bromo-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-butyramide;
N-(2-Chloro-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-2-(3-fluoro-phenyl)-acetamide;
N-(2-Chloro-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-2-cyclopentyl-acetamide;
 10 2-Cyclopentyl-*N*-(2,6-dimethyl-4-[2-(4-trifluoromethyl-phenyl)-morpholin-4-yl]-phenyl)-acetamide;
N-(4-[2-(2-Chloro-phenyl)-morpholin-4-yl]-2,6-dimethyl-phenyl)-2-cyclopentyl-acetamide;
 2-Cyclopentyl-*N*-(4-[2-(4-fluoro-phenyl)-morpholin-4-yl]-2,6-dimethyl-phenyl)-acetamide;
 15 *N*-(2-Chloro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;
 Pentanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;
 4-Methyl-pentanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;
 2-Cyclopent-2-enyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;
 20 5-Methyl-hexanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;
 3-Methyl-pentanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;
 Hex-5-enoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;
 3-Ethyl-pentanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;
 2-Cyclopentyl-*N*-(4-morpholin-4-yl-2-pyridin-3-yl-6-trifluoromethyl-phenyl)-acetamide;
 25 *N*-(5-morpholin-4-yl-3-trifluoromethyl-biphenyl-2-yl)-acetamide;
 2-Cyclopentyl-*N*-(4'-fluoro-5-morpholin-4-yl-3-trifluoromethyl-biphenyl-2-yl)-acetamide;
 2-Cyclopentyl-*N*-(4'-methyl-5-morpholin-4-yl-3-trifluoromethyl-biphenyl-2-yl)-acetamide;
 30 *N*-(3'-methyl-5-morpholin-4-yl-3-trifluoromethyl-biphenyl-2-yl)-acetamide;
 2-Cyclopentyl-*N*-(3',4'-difluoro-5-morpholin-4-yl-3-trifluoromethyl-biphenyl-2-yl)-acetamide;

- 2-(4-Fluoro-phenyl)-*N*-(4-morpholin-4-yl-2-pyridin-3-yl-6-trifluoromethyl-phenyl)-acetamide;
 2-Cyclopentyl-*N*-(2,6-diethyl-4-morpholin-4-yl-phenyl)-acetamide;
 2-Cyclopentyl-*N*-(2,6-diisopropyl-4-morpholin-4-yl-phenyl)-acetamide;
 5 2-Cyclopentyl-*N*-(2,6-difluoro-4-morpholin-4-yl-phenyl)-acetamide;
 Hexanoic acid (2,6-difluoro-4-morpholin-4-yl-phenyl)-amide;
N-(2,6-Difluoro-4-morpholin-4-yl-phenyl)-3,3-dimethyl-butyramide;
N-(2,6-Difluoro-4-morpholin-4-yl-phenyl)-2-(3-fluoro-phenyl)-acetamide;
 2-Cyclopent-2-enyl-*N*-(2,6-difluoro-4-morpholin-4-yl-phenyl)-acetamide;
 10 2-Bicyclo[2.2.1]hept-2-yl-*N*-(2,6-difluoro-4-morpholin-4-yl-phenyl)-acetamide;
 2-Bicyclo[2.2.1]hept-2-yl-*N*-(2-methyl-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-acetamide;
 5-Methyl-pentanoic acid (2-methyl-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-amide;
 15 5-Methyl-hexanoic acid (2-methyl-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-amide;
 2-Cyclopent-2-enyl-*N*-(2-methyl-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-acetamide;
 2-Cyclopentyl-*N*-(2-methyl-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-acetamide;
 Hexanoic acid (2-methyl-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-amide;
 20 3,3-Dimethyl-*N*-(2-methyl-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-butyramide;
 2-(3,4-Difluoro-phenyl)-*N*-(2-methyl-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-acetamide;
 Hexanoic acid (2-methoxy-6-methyl-4-morpholin-4-yl-phenyl)-amide;
 2-Cyclopentyl-*N*-(2-methoxy-6-methyl-4-morpholin-4-yl-phenyl)-acetamide;
 25 *N*-(2-Methoxy-6-methyl-4-morpholin-4-yl-phenyl)-3,3-dimethyl-butyramide;
 2-(3,4-Difluoro-phenyl)-*N*-(2-methoxy-6-methyl-4-morpholin-4-yl-phenyl)-acetamide;
 2-Cyclopent-2-enyl-*N*-(2-methoxy-6-methyl-4-morpholin-4-yl-phenyl)-acetamide;
 2-(3-Fluoro-phenyl)-*N*-(2-methoxy-6-methyl-4-morpholin-4-yl-phenyl)-acetamide;
 2-Bicyclo[2.2.1]hept-2-yl-*N*-(2-methoxy-6-methyl-4-morpholin-4-yl-phenyl)-acetamide;
 30 *N*-(2-methoxy-6-methyl-4-morpholin-4-yl-phenyl)-amide;
 5-Methyl-hexanoic acid (2-methoxy-6-methyl-4-morpholin-4-yl-phenyl)-amide;
N-(2-Chloro-6-methyl-4-morpholin-4-yl-phenyl)-2-(3-fluoro-phenyl)-acetamide; and
N-(2-Chloro-6-methyl-4-morpholin-4-yl-phenyl)-2-cyclopentyl-acetamide;

as the free base or a salt thereof. Each of these compounds is considered a specific embodiment and may be subjected to individual claims.

The present invention also comprises salts of the compounds of the invention, typically, pharmaceutically acceptable salts. The salts of the invention include acid addition salts, metal salts, ammonium and alkylated ammonium salts.

The salts of the invention are preferably acid addition salts. The acid addition salts of the invention are preferably pharmaceutically acceptable salts of the compounds of the invention formed with non-toxic acids. Acid addition salts include salts of inorganic acids as well as organic acids. Examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like. Examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halothephyllines, for example 8-bromothephylline and the like. Further examples of pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977,66,2, which is incorporated herein by reference.

Also intended as acid addition salts are the hydrates, which the present compounds, are able to form.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

In one embodiment, the compounds are KCNQ2 active with an EC_{50} of less than 15000 nM such as less than 10000 nM as measured by the test "Relative efflux through the KCNQ2 channel". In another embodiment, the compounds are KCNQ2 active with an EC_{50} of less than 2000 nM such as less than 1500 nM as measured by the test "Relative efflux through the KCNQ2 channel". In yet another embodiment, the compounds are KCNQ2 active with an EC_{50} of less than 200 nM such as less than 150 nM as measured by the test "Relative efflux through the KCNQ2 channel". The test "Relative efflux through the KCNQ2 channel" is described below.

In one embodiment, the compounds have an ED_{50} of less than 15 mg/kg in the test "Maximum electroshock". In another embodiment, the compounds have an ED_{50} of less than 5 mg/kg in the test "Maximum electroshock". The test "Maximum electroshock" is described below.

In one embodiment, the compounds have an ED_{50} of less than 5 mg/kg in the "Electrical seizure -threshold test" and "Chemical seizure -threshold test" which are described below.

Some compounds have few or clinically insignificant side effects. Some of the compounds are thus tested in models of the unwanted sedative, hypothermic and ataxic actions of the compounds.

Some of the compounds have a large therapeutic index between anticonvulsant efficacy and side-effects such as impairment of locomotor activity or ataxic effects as measured by performance on a rotating rod. Such compounds will expectedly be well tolerated in patients permitting high doses to be used before side effects are seen. Thereby compliance with the therapy will expectedly be good and administration of high doses may be permitted making the treatment more efficacious in patients who would otherwise have side effects with other medications.

A non-limiting aspect of the invention concerns compounds according to below embodiments 1-10:

1. A substituted morpholine or thiomorpholine derivative of the general formula I

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1. The first part of the report is a general introduction to the project. It describes the purpose of the study and the objectives that were set at the beginning of the project.

2. The second part of the report is a detailed description of the methodology used in the study. It includes information about the data sources, the sampling method, and the statistical techniques that were used to analyze the data.

3. The third part of the report is a discussion of the results of the study. It presents the findings of the research and discusses their implications for the field of study.

4. The fourth part of the report is a conclusion that summarizes the main findings of the study and provides recommendations for future research.

5. The fifth part of the report is a list of references that includes all of the sources that were used in the study.

6. The sixth part of the report is an appendix that contains additional information that is relevant to the study but that is not included in the main body of the report.

7. The seventh part of the report is a glossary that defines the key terms and concepts that are used in the study.

8. The eighth part of the report is a list of figures and tables that are included in the study.

9. The ninth part of the report is a list of footnotes that provide additional information about the sources used in the study.

10. The tenth part of the report is a list of appendices that contain additional information that is relevant to the study but that is not included in the main body of the report.

11. The eleventh part of the report is a list of references that includes all of the sources that were used in the study.

12. The twelfth part of the report is a conclusion that summarizes the main findings of the study and provides recommendations for future research.

13. The thirteenth part of the report is a list of figures and tables that are included in the study.

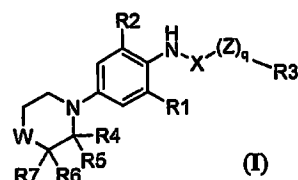
14. The fourteenth part of the report is a list of footnotes that provide additional information about the sources used in the study.

15. The fifteenth part of the report is a list of appendices that contain additional information that is relevant to the study but that is not included in the main body of the report.

16. The sixteenth part of the report is a glossary that defines the key terms and concepts that are used in the study.

17. The seventeenth part of the report is a list of figures and tables that are included in the study.

18. The eighteenth part of the report is a list of footnotes that provide additional information about the sources used in the study.



wherein

q is 0 or 1;

W is O or S;

X is CO;

Z is O;

R1 and R2 are independently selected from the group consisting of halogen, halo-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl and cyano;

R3 is selected from the group consisting of C₁₋₁₀-alk(en/yn)yl,

C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, Ar-C₁₋₆-alk(en/yn)yl and Ar; and

R4, R5, R6 and R7 are independently selected from the group consisting of hydrogen and Ar;

as the free base or salts thereof.

2. A compound according to embodiment 1, said compound being selected from the group consisting of:

N-(2-Bromo-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-2-(4-fluoro-phenyl)-acetamide;

2-Cyclopentyl-*N*-(2-bromo-6-trifluoromethyl-4-morpholin-4-yl-phenyl)-acetamide;

N-(2-Bromo-4-morpholin-4-yl-6-trifluoromethyl-phenyl)-3-cyclopentyl-propionamide;

N-(2-Chloro-6-cyano-4-morpholin-4-yl-phenyl)-3-cyclohexyl-propionamide;

2-Cyclopentyl-*N*-(2,6-dimethyl-4-thiomorpholin-4-yl-phenyl)-acetamide;

2-Cyclopentyl-*N*-[2,6-dimethyl-4-(2-phenyl-morpholin-4-yl)-phenyl]-acetamide;

2-Cyclopentyl-*N*-[2,6-dimethyl-4-(2-phenyl-thiomorpholin-4-yl)-phenyl]-acetamide;

2-Cyclopentyl-*N*-[2,6-dimethyl-4-(3-pyridin-3-yl-thiomorpholin-4-yl)-phenyl]-acetamide;

2-Cyclopentyl-*N*-[2,6-dimethyl-4-[2-(4-trifluoromethyl-phenyl)-thiomorpholin-4-yl]-phenyl]-acetamide;

N-(4-[2-(2-Chloro-phenyl)-thiomorpholin-4-yl]-2,6-dimethyl-phenyl)-2-cyclopentyl-acetamide;

2-Bicyclo[2.2.1]hept-2-yl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

2-Cyclohexyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

3-(3,4-Difluoro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-propionamide;

2-Cyclopentyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-carbamic acid butyl ester;

2-(4-Chloro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

2,3-Dihydro-benzofuran-2-carboxylic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;

3-Cyclohexyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-propionamide;

3-Cyclopentyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-propionamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-(4-fluoro-phenyl)-acetamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-thiophen-2-yl-acetamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-3,3-dimethyl-butylamide;

Hexanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;

2-Cycloheptyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-carbamic acid benzyl ester;

(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-carbamic acid 2-chloro-benzyl ester;

3,5,5-Trimethyl-hexanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;

Octanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;

Heptanoic acid (2,6-dimethyl-4-morpholin-4-yl-phenyl)-amide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-phenyl-acetamide

2-(3,4-Dichloro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

2-(4-Allyloxy-3-chloro-phenyl)-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-(3-trifluoromethyl-phenyl)-acetamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-naphthalen-2-yl-acetamide;

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3-(3-Chloro-phenyl)-N-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-propionamide;

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-(3,4-dimethyl-phenyl)-acetamide;

- 5 *2-(3-Bromo-phenyl)-N-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;*
2-(3-Chloro-phenyl)-N-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;
N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-p-tolyl-acetamide;
N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-m-tolyl-acetamide;
2-(3,4-Difluoro-phenyl)-N-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide;
 10 *and*

N-(2,6-Dimethyl-4-morpholin-4-yl-phenyl)-2-(3-fluoro-phenyl)-acetamide.

3. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and one or more compounds according to any one of embodiments 1 and 2.
- 15 4. Use of a pharmaceutical composition according to embodiment 3 for increasing ion flow in a voltage-dependent potassium channel of a mammal such as a human.
5. Use according to embodiment 4 in the treatment of a disorder or disease being responsive to an increased ion flow in a voltage-dependent potassium channel,
- 20 such disorder or disease is preferably a disorder or diseases of the central nervous system.
6. Use according to embodiment 5 characterized in that the disorder or disease is selected from the group consisting of seizure disorders such as convulsions, epilepsy and status epilepticus.
- 25 7. Use according to embodiment 5 characterized in that the disorder or disease is selected from the group consisting of neuropathic and migraine pain disorders such as allodynia, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathy and neuropathic pain related to migraine.
8. Use according to embodiment 5 characterized in that the disorder or disease is
- 30 selected from the group consisting of anxiety disorders such as anxiety, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety

disorder, agoraphobia, specific phobias, anxiety disorder due to general medical condition and substance-induced anxiety disorder.

9. Use according to embodiment 5 characterized in that the disorder or disease is selected from the group consisting of neurodegenerative disorders such as
- 5 Alzheimer's disease, Huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis, AIDS-induced encephalopathy and other infection-related encephalopathies being caused by rubella viruses, herpes viruses, borrelia and by unknown pathogens, Creutzfeld-Jakob disease, Parkinson's disease, trauma-induced neurodegenerations.
- 10 10. Use according to embodiment 5 characterized in that the disorder or disease is selected from the group consisting of neuronal hyperexcitation states such as in medicament withdrawal or by intoxication.

15 Definitions

The term heteroatom refers to a nitrogen, oxygen or sulphur atom.

Halogen means fluoro, chloro, bromo or iodo.

- 20 The expression C₁₋₆-alk(en/yn)yl means a C₁₋₆-alkyl, C₂₋₆-alkenyl or a C₂₋₆-alkynyl group. The term C₁₋₆-alkyl refers to a branched or un-branched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl. Similarly, C₂₋₆-alkenyl and C₂₋₆-alkynyl, respectively, designate such groups having
- 25 from two to six carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.
- The expression C₁₋₁₀-alk(en/yn)yl means a C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl or a C₂₋₁₀-alkynyl
- 30 group. The term C₁₋₁₀-alkyl refers to a branched or un-branched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 1-pentyl, 1-hexyl, 1-heptyl, 1-octyl, 1-nonyl, 1-decyl, 2-methyl-2-propyl and 2-methyl-1-propyl. Similarly, C₂₋₁₀-alkenyl and C₂₋₁₀-alkynyl, respectively, designate such groups having from two to six carbon

atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, and decynyl.

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The expression C₃₋₈-cycloalk(en)yl means a C₃₋₈-cycloalkyl- or cycloalkenyl group. The term C₃₋₈-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, [1.1.1]bicyclopentyl, bicyclo[2.2.1]heptyl, [2.2.2]bicyclooctyl and [3.3.0]bicyclooctyl, etc. The term C₃₋₈-cycloalkenyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

10

The term halo-C₁₋₆-alk(en/yn)yl designates C₁₋₆-alk(en/yn)yl being substituted with one or more halogen atoms, including but not limited to trifluoromethyl. Similarly, halo-C₃₋₈-cycloalk(en)yl designates C₃₋₈-cycloalk(en)yl being substituted with one or more halogen atoms. In the expression halo-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl the terms C₁₋₆-alk(en/yn)yl and halo-C₃₋₈-cycloalk(en)yl are as defined above.

20

When two adjacent substituents together with the aromatic group to which they are attached form a 4-8 membered ring, which optionally contains one, two or three heteroatoms, then a ring system is formed by 4-8 atoms selected from 4-8 carbonatoms and 0-3 heteroatoms selected from N, S, or O. Such two adjacent

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substituents may together form:
 -(CH₂)_a-CH₂-, -CH=CH-(CH₂)_b-, -CH₂-CH=CH-(CH₂)_c-, -CH=CH-CH=CH-,
 -(CH₂)_a-O-, -O-(CH₂)_b-O-, -CH₂-O-(CH₂)_c-O-, -CH₂-O-CH₂-O-CH₂-,
 -(CH₂)_a-S-, -S-(CH₂)_b-S-, -CH₂-S-(CH₂)_c-S-, -CH₂-S-CH₂-S-CH₂-,
 -(CH₂)_a-NH-, -NH-(CH₂)_b-NH-, -CH₂-NH-(CH₂)_c-NH-, -CH=CH-NH-,
 -O-(CH₂)_b-NH-, -CH₂-O-(CH₂)_c-NH- or -O-(CH₂)_c-NH-CH₂-, -S-(CH₂)_b-NH-,
 -N=CH-NH-, -N=CH-O- or -N=CH-S- or -N=N-NH-,
 wherein b is 1, 2 or 3, a is 2, 3 or 4 and c is 1 or 2.

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The term Ar refers to optionally substituted aromatic systems of 5-10 carbon atoms, wherein 0, 1, 2, 3 or 4 carbon atoms may be replaced by heteroatoms independently selected from N, S, or O. Examples of such Ar groups are optionally substituted phenyl, optionally substituted naphthyl, optionally substituted pyridine, optionally substituted thiophene, optionally substituted furan, optionally substituted thiazole, optionally substituted quinoline, optionally substituted indole, optionally substituted 2,3-dihydro-benzofuran, optionally substituted pyrimidine, optionally substituted pyrrole and optionally substituted oxazole. Ar may be substituted with one or more substituents independently being hydroxy, halogen, C₁₋₆-alk(en/yn)yl,

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C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl, C₃₋₈-alk(en/yn)yl, acyl, nitro or cyano, -CO-NH-C₁₋₆-alk(en/yn)yl, -CO-N(C₁₋₆-alk(en/yn)yl)₂, -NH₂, -NH-C₁₋₆-alk(en/yn)yl, -N(C₁₋₆-alk(en/yn)yl)₂, -S-C₁₋₆-alk(en/yn)yl, -SO₂-C₁₋₆-alk(en/yn)yl, -SO₂N(C₁₋₆-alk(en/yn)yl)₂ and -SO₂NH-C₁₋₆-alk(en/yn)yl; or two adjacent substituents may together with the aromatic group to which they are attached form a 4-8 membered ring, which optionally contains one, two or three heteroatoms.

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When Ar is substituted with CO-NH-C₁₋₆-alk(en/yn)yl or CO-N(C₁₋₆-alk(en/yn)yl)₂, then the carbon atom of the CO group is attached to Ar.

When Ar is substituted with NH₂, NH-C₁₋₆-alk(en/yn)yl or N(C₁₋₆-alk(en/yn)yl)₂, then the nitrogen atom is attached to Ar.

When Ar is substituted with -S-C₁₋₆-alk(en/yn)yl, -SO₂-C₁₋₆-alk(en/yn)yl, -SO₂N(C₁₋₆-alk(en/yn)yl)₂ or -SO₂NH-C₁₋₆-alk(en/yn)yl then the sulphur atom is attached to Ar.

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The term acyl refers to formyl, C₁₋₆-alk(en/yn)ylcarbonyl, C₃₋₈-cycloalk(en)ylcarbonyl, Ar-carbonyl, Ar-C₁₋₆-alk(en/yn)ylcarbonyl or a C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl-carbonyl group, wherein C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl and Ar are as defined above.

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The terms C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, Ar-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl and C₃₋₈-cycloalk(en)yl; designate such groups in which the C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl and Ar are as defined above. Similarly, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl oxy designate such groups in which C₃₋₈-cycloalk(en)yl and C₁₋₆-alk(en/yn)yl oxy are as defined above.

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The expressions Ar-C₃₋₈-cycloalk(en)yl and Ar-C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl designate such groups in which the C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl and Ar are as defined above.

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Pharmaceutical compositions

The present invention also relates to a pharmaceutical composition. The compounds of the invention or salts thereof may be administered alone or in combination with pharmaceutically acceptable carriers or diluents, in either single or multiple doses.

10 The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

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The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and

20 intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the disorder or disease to be treated and the active ingredient chosen.

25 The pharmaceutical compositions formed by combining the compound of the invention and the pharmaceutical acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

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The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the invention contains a free base such salts are prepared in a conventional manner by treating a

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solution or suspension of a free base of the invention with a chemical equivalent of a pharmaceutically acceptable acid. Representative examples are mentioned above.

Pharmaceutical compositions for oral administration may be solid or liquid. Solid dosage forms for oral administration include e.g. capsules, tablets, dragees, pills, lozenges, powders, granules and tablette e.g. placed in a hard gelatine capsule in powder or pellet form or e.g. in the form of a troche or lozenge. Where appropriate, pharmaceutical compositions for oral administration may be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release

10 of the active ingredient such as sustained or prolonged release according to methods well known in the art. Liquid dosage forms for oral administration include e.g. solutions, emulsions, suspensions, syrups and elixirs.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

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Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid, lower alkyl ethers of cellulose, corn starch, potato starch, gums and the like. Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water.

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The carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

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Any adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

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1. The first part of the report is a summary of the work done during the year.

2. The second part is a detailed account of the work done during the year.

3. The third part is a summary of the work done during the year.

4. The fourth part is a summary of the work done during the year.

5. The fifth part is a summary of the work done during the year.

6. The sixth part is a summary of the work done during the year.

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